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 NEWS  4  OCT 07  Multiple databases enhanced for more flexible patent
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 NEWS  5  OCT 22  Current-awareness alert (SDI) setup and editing
                  enhanced
 NEWS  6  OCT 22  WPIDS, WPINDEX, and WPIX enhanced with Canadian PCT
                  Applications
 NEWS  7  OCT 24  CHEMLIST enhanced with intermediate list of
                  pre-registered REACH substances
 NEWS  8  NOV 21  CAS patent coverage to include exemplified prophetic
                  substances identified in English-, French-, German-,
                  and Japanese-language basic patents from 2004-present
 NEWS  9  NOV 26  MARPAT enhanced with FSORT command
 NEWS 10  NOV 26  MEDLINE year-end processing temporarily halts
                  availability of new fully-indexed citations
 NEWS 11  NOV 26  CHEMSAFE now available on STN Easy
 NEWS 12  NOV 26  Two new SET commands increase convenience of STN
                  searching
 NEWS 13  DEC 01  ChemPort single article sales feature unavailable
 NEWS 14  DEC 12  GBFULL now offers single source for full-text
                  coverage of complete UK patent families
 NEWS 15  DEC 17  Fifty-one pharmaceutical ingredients added to PS

 NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,
              AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

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COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.22       0.22

FILE 'MEDLINE' ENTERED AT 12:57:51 ON 05 JAN 2009

FILE 'SCISEARCH' ENTERED AT 12:57:51 ON 05 JAN 2009
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=> s asparaginyl endopeptidase
L1          271 ASPARAGINYL ENDOPEPTIDASE

=> s inhibit?
L2      4097762 INHIBIT?

=> s l1 and l2
L3          114 L1 AND L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4           63 DUP REM L3 (51 DUPLICATES REMOVED)

=> d ibib abs 1-63

L4   ANSWER 1 OF 63     MEDLINE on STN                  DUPLICATE 1
ACCESSION NUMBER:    2008290626     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 18249028
TITLE:               Cystatins from filarial parasites: evolution, adaptation
                     and function in the host-parasite relationship.
AUTHOR:              Gregory William F; Maizels Rick M
CORPORATE SOURCE:    Institute of Immunology and Infection Research, Ashworth
                     Laboratories, University of Edinburgh, West Mains Road,
                     Edinburgh EH9 3JT, UK.
CONTRACT NUMBER:      (United Kingdom Wellcome Trust)
SOURCE:              The international journal of biochemistry & cell biology,
                     (2008) Vol. 40, No. 6-7, pp. 1389-98.  Electronic
                     Publication: 2007-12-04. Ref: 46
                     Journal code: 9508482. ISSN: 1357-2725.
PUB. COUNTRY:        England: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     (RESEARCH SUPPORT, NON-U.S. GOV'T)
                     General Review; (REVIEW)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200808
ENTRY DATE:          Entered STN: 6 May 2008
                     Last Updated on STN: 14 Aug 2008
                     Entered Medline: 13 Aug 2008
AB   Cystatins, together with stefins and kininogens, are members of the
     cystatin superfamily of cysteine protease inhibitors (CPI)
     present across the animal and plant kingdoms.  Their role in parasitic
     organisms may encompass both essential developmental processes and
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specific interactions with the parasite's vector and/or final host. We summarise information gathered on three cystatins from the human filarial nematode Brugia malayi (Bm-CPI-1, -2 and -3), and contrast them those expressed by other parasites and by the free-living nematode Caenorhabditis elegans. Bm-CPI-2 differs from C. elegans cystatin, having acquired the additional function of inhibiting asparaginyl endopeptidase (AEP), in a manner similar to some human cystatins. Thus, we propose that Bm-CPI-2 and orthologues from related filarial parasites represent a new subset of nematode cystatins. Bm-CPI-1 and CPI-3 share only 25% amino acid identity with Bm-CPI-2, and lack an evolutionarily conserved glycine residue in the N-terminal region. These sequences group distantly from the other nematode cystatins, and represent a second novel subset of filarial cystatin-like genes. Expression analyses also show important differences between the CPI-2 and CPI-1/-3 groups. Bm-cpi-2 is expressed at all time points of the parasite life cycle, while Bm-cpi-1 and -3 expression is confined to the late stages of development in the mosquito vector, terminating within 48h of infection of the mammalian host. Hence, we hypothesise that CPI-2 has evolved to block mammalian proteases (including the antigen-processing enzyme AEP) while CPI-1 and -3 function in the milieu of the mosquito vector necessary for transmission of the parasite.

L4 ANSWER 2 OF 63 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2008189338 MEDLINE
DOCUMENT NUMBER: PubMed ID: 18222467
TITLE: H1Lgm2, a member of asparaginyl endopeptidases/legumains in the midgut of the ixodid tick Haemaphysalis longicornis, is involved in blood-meal digestion.
AUTHOR: Alim M Abdul; Tsuji Naotoshi; Miyoshi Takeharu; Islam M Khyrul; Huang Xiaohong; Hatta Takeshi; Fujisaki Kozo
CORPORATE SOURCE: Laboratory of Parasitic Diseases, National Institute of Animal Health, National Agricultural and Food Research Organization, Tsukuba, Ibaraki 305-0856, Japan.
SOURCE: Journal of insect physiology, (2008 Mar) Vol. 54, No. 3, pp. 573-85. Electronic Publication: 2007-12-23. Journal code: 2985080R. ISSN: 0022-1910.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200807
ENTRY DATE: Entered STN: 20 Mar 2008
Last Updated on STN: 25 Jul 2008
Entered Medline: 24 Jul 2008

AB Here we describe a cDNA encoding the second asparaginyl endopeptidase/legumain (H1Lgm2) from the midgut of the ixodid tick Haemaphysalis longicornis. Endogenous H1Lgm2 was expressed in all the developmental stages of the tick, localized mainly in the midgut epithelium and was up-regulated by the host blood-feeding process, as demonstrated by immunoblotting and immunohistochemistry. RT-PCR and real-time PCR showed that the H1Lgm2 gene was expressed at a lower level during all phases of blood-feeding than our previously characterized legumain (H1Lgm) gene from the same tick. More strikingly, there was no expression of H1Lgm2 mRNA beyond 96 h of blood-feeding, while H1Lgm mRNA expression continued until full engorgement. Escherichia coli-expressed recombinant H1Lgm2 (rH1Lgm2) efficiently hydrolysed the legumain-specific synthetic substrate. rH1Lgm2 activity was inhibited by iodoacetamide and N-ethylmaleimide and also by Fe(2+), Cu(2+), Co(2+) and Ni(2+). rH1Lgm2 digested bovine haemoglobin and exhibited strict specificity for the asparaginyl bonds on the carboxy-terminal side of a peptide, as demonstrated by internal amino acid sequence analysis of the

cleaved bovine serum albumin products. Our results suggest that HlLgm2, together with HlLgm, plays a pivotal role in host blood-meal digestion process.

L4 ANSWER 3 OF 63 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2008058974 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17786443
TITLE: A Legumain-based minigene vaccine targets the tumor stroma and suppresses breast cancer growth and angiogenesis.
AUTHOR: Lewen Susanna; Zhou He; Hu Huai-dong; Cheng Tingmei; Markowitz Dorothy; Reisfeld Ralph A; Xiang Rong; Luo Yunping
CORPORATE SOURCE: Department of Immunology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.
SOURCE: Cancer immunology, immunotherapy : CII, (2008 Apr) Vol. 57, No. 4, pp. 507-15. Electronic Publication: 2007-09-05. Journal code: 8605732. ISSN: 0340-7004.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200805
ENTRY DATE: Entered STN: 29 Jan 2008
Last Updated on STN: 22 May 2008
Entered Medline: 21 May 2008

AB Tumor associated macrophages (TAMs) are well known to play a very important role in tumor angiogenesis and metastasis. The suppression of TAMs in the tumor-microenvironment (TME) provides a novel strategy to inhibit tumor growth and dissemination by remodeling the tumor's stroma. Here, we tested our hypothesis that suppression of TAMs can be achieved in syngeneic BALB/c mice with oral minigene vaccines against murine MHC class I antigen epitopes of Legumain, an asparaginyl endopeptidase and a member of the C13 family of cystine proteases which is overexpressed on TAMs in the tumor stroma. Vaccine vectors were constructed and transformed into attenuated Salmonella typhimurium (Dam (-) , AroA (-)) for oral delivery. Groups of mice received either the expression vectors encoding the Legumain H-2D or 2K epitopes or the control empty vector by gavage. The efficacy of the minigene vaccines was determined by their ability to protect mice from lethal tumor cell challenges, the induction of a specific CTL response as well as IFN-gamma release, and inhibition of tumor angiogenesis. We demonstrated that the Legumain minigene vaccine provided effective protection against tumor cell challenge by inducing a specific CD8+ T-cell response against Legumain+ TAMs in our breast tumor model. The protection, induced by this T-cell response, mediated by the Legumain Kd minigene, is also responsible for lysing D2F2 breast carcinoma cells in syngeneic BALB/c mice and for suppressing tumor angiogenesis. Importantly, in a prophylactic setting, the minigene vaccine proved to be of similar anti-tumor efficacy as a vaccine encoding the entire Legumain gene. Together, our findings establish proof of concept that a Legumain minigene vaccine provides a more flexible alternative to the whole gene vaccine, which may facilitate the future design and clinical applications of such a vaccine for cancer prevention.

L4 ANSWER 4 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2008:922417 SCISEARCH
THE GENUINE ARTICLE: 326UP
TITLE: The origin and evolution of plant cystatins and their target cysteine proteinases indicate a complex functional relationship

AUTHOR: Martinez, Manuel (Reprint)
CORPORATE SOURCE: Univ Politecn Madrid, Ctr Biotecnol & Genom Plantas, Dpto Biotecnol, Lab Bioquim & Biol Mol, ETS Ingn Agronomos, Ciudad Univ S-N, E-28040 Madrid, Spain (Reprint)
AUTHOR: Diaz, Isabel
CORPORATE SOURCE: Univ Politecn Madrid, Ctr Biotecnol & Genom Plantas, Dpto Biotecnol, Lab Bioquim & Biol Mol, ETS Ingn Agronomos, E-28040 Madrid, Spain
E-mail: m.martinez@upm.es; i.diaz@upm.es
COUNTRY OF AUTHOR: Spain
SOURCE: BMC EVOLUTIONARY BIOLOGY, (10 JUL 2008) Vol. 8, arn. 198. ISSN: 1471-2148.
PUBLISHER: BIOMED CENTRAL LTD, CURRENT SCIENCE GROUP, MIDDLESEX HOUSE, 34-42 CLEVELAND ST, LONDON W1T 4LB, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 72
ENTRY DATE: Entered STN: 1 Aug 2008
Last Updated on STN: 1 Aug 2008
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Cystatins and their putative targets, the families of cysteine proteinases C1A and C13 play key roles in plants. Comparative genomic analyses are powerful tools to obtain valuable insights into the conservation and evolution of the proteinases and their proteinaceous inhibitors, and could aid to elucidate issues concerning the function of these proteins.

Results: We have performed an evolutionary comparative analysis of cysteine proteinases C1A and C13 and their putative inhibitors in representative species of different taxonomic groups that appeared during the evolution of the Viridiplantae. The results indicate that whereas C1A cysteine proteinases are present in all taxonomic groups, cystatins and C13 cysteine proteinases are absent in some basal groups. Moreover, gene duplication events have been associated to the increasing structural and functional complexities acquired in land plants.

Conclusion: Comparative genomic analyses have provided us valuable insights into the conservation and evolution of the cystatin inhibitory family and their putative targets, the cysteine proteinases from families C1A and C13. Functionality of both families of proteins in plants must be the result of a coevolutionary process that might have occurred during the evolution of basal and land plants leading to a complex functional relationship among them.

L4 ANSWER 5 OF 63 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2008146776 EMBASE
TITLE: Oral DNA vaccines target the tumor vasculature and microenvironment and suppress tumor growth and metastasis.
AUTHOR: Reisfeld, Ralph A.
CORPORATE SOURCE: Scripps Research Institute, Department of Immunology, 10550 N. Torrey Pines Rd., San Diego, CA 92037, United States. reisfeld@scripps.edu
AUTHOR: Xiang, Rong; Luo, Yunping; Reisfeld, Ralph A.
CORPORATE SOURCE: Department of Immunology, Scripps Research Institute, San Diego, CA, United States. reisfeld@scripps.edu
AUTHOR: Niethammer, Andreas G.
CORPORATE SOURCE: Pfizer Inc., San Diego, CA, United States.
AUTHOR: Reisfeld, R. A. (correspondence)
CORPORATE SOURCE: Scripps Research Institute, Department of Immunology, 10550 N. Torrey Pines Rd., San Diego, CA 92037, United States. reisfeld@scripps.edu
SOURCE: Immunological Reviews, (Apr 2008) Vol. 222, No. 1, pp. 117-128.

Refs: 54
ISSN: 0105-2896 E-ISSN: 1600-065X CODEN: IMRED2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 25 Apr 2008
Last Updated on STN: 25 Apr 2008

AB Four novel oral DNA vaccines provide protection against melanoma, colon, breast, and lung carcinoma in mouse models. Vaccines are delivered by attenuated Salmonella typhimurium to secondary lymphoid organs and respectively target vascular endothelial growth factor receptor-2, transcription factor Fos-related antigen-1, anti-apoptosis protein survivin and Legumain, an asparaginyl endopeptidase specifically overexpressed on tumor-associated macrophages (TAMs) in the tumor microenvironment (TME). These vaccines are all capable of inducing potent cell-mediated protective immunity against self-antigens, resulting in marked suppression of tumor growth and dissemination. Key mechanisms induced by these DNA vaccines include efficient suppression of angiogenesis in the tumor vasculature and marked activation of cytotoxic T cells, natural killer cells, and antigen-presenting dendritic cells. The vaccine targeting Legumain establishes the new paradigm whereby a reduction in the density of TAMs in the TME decreases the release of factors potentiating tumor growth and angiogenesis. This, in turn, remodels the TME and decreases its immunosuppressive milieu and thereby potentiates the DNA vaccine's ability to effectively suppress tumor cell proliferation, vascularization, and metastasis. It is anticipated that such research efforts will lead to novel DNA-based vaccines that will be effective for the treatment of cancer. .COPYRGT. 2008 The Authors.

L4 ANSWER 6 OF 63 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2007580442 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17698845
TITLE: An asparaginyl endopeptidase mediates in vivo protein backbone cyclization.
AUTHOR: Saska Ivana; Gillon Amanda D; Hatsugai Noriyuki; Dietzgen Ralf G; Hara-Nishimura Ikuko; Anderson Marilyn A; Craik David J
CORPORATE SOURCE: Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland 4072, Australia.
SOURCE: The Journal of biological chemistry, (2007 Oct 5) Vol. 282, No. 40, pp. 29721-8. Electronic Publication: 2007-08-13. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200711
ENTRY DATE: Entered STN: 2 Oct 2007
Last Updated on STN: 8 Nov 2007
Entered Medline: 7 Nov 2007

AB Proteases can catalyze both peptide bond cleavage and formation, yet the hydrolysis reaction dominates in nature. This presents an interesting challenge for the biosynthesis of backbone cyclized (circular) proteins, which are encoded as part of precursor proteins and require post-translational peptide bond formation to reach their mature form. The largest family of circular proteins are the plant-produced cyclotides;

extremely stable proteins with applications as bioengineering scaffolds. Little is known about the mechanism by which they are cyclized in vivo but a highly conserved Asn (occasionally Asp) residue at the C terminus of the cyclotide domain suggests that an enzyme with specificity for Asn (asparaginyl endopeptidase; AEP) is involved in the process. Nicotiana benthamiana does not endogenously produce circular proteins but when cDNA encoding the precursor of the cyclotide kalata B1 was transiently expressed in the plants they produced the cyclotide, together with linear forms not commonly observed in cyclotide-containing plants. Observation of these species over time showed that in vivo asparaginyl bond hydrolysis is necessary for cyclization. When AEP activity was suppressed, either by decreasing AEP gene expression or using a specific inhibitor, the amount of cyclic cyclotide in the plants was reduced compared with controls and was accompanied by the accumulation of extended linear species. These results suggest that an AEP is responsible for catalyzing both peptide bond cleavage and ligation of cyclotides in a single processing event.

L4 ANSWER 7 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2007:805061 SCISEARCH
THE GENUINE ARTICLE: 185FA
TITLE: Carboxy terminal extended phytocystatins are bifunctional inhibitors of papain and legumain cysteine proteinases
AUTHOR: Martinez, Manuel (Reprint)
CORPORATE SOURCE: Univ Politecn Madrid, Ctr Biotecnol & Genom Plantas, Dept Biotechnol, Lab Bioquim & Biol Mol, ETS Ingn Agronomos, Ciudad Univ S-N, E-28040 Madrid, Spain (Reprint)
AUTHOR: Diaz-Mendoza, Mercedes; Carrillo, Laura; Diaz, Isabel
CORPORATE SOURCE: Univ Politecn Madrid, Ctr Biotecnol & Genom Plantas, Dept Biotechnol, Lab Bioquim & Biol Mol, ETS Ingn Agronomos, E-28040 Madrid, Spain
E-mail: m.martinez@upm.es
COUNTRY OF AUTHOR: Spain
SOURCE: FEBS LETTERS, (26 JUN 2007) Vol. 581, No. 16, pp. 2914-2918.
ISSN: 0014-5793.
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 24
ENTRY DATE: Entered STN: 6 Sep 2007
Last Updated on STN: 6 Sep 2007

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Plant legumains are cysteine proteinases putatively involved in processing endogenous proteins. Phytocystatins (Phy-Cys) have been described as plant inhibitors of papain-like cysteine proteinases. Some PhyCys contain a carboxy terminal extension with an amino acid motif (SNSL) similar to that involved in the inhibition of legumain-like proteins by human cystatins. The role of these carboxy terminal extended PhyCys as inhibitors of legumain-like cysteine proteinases is here shown by in vitro inhibition of human legumain and legumain-like activities from barley extracts. Moreover, site-directed mutagenesis has demonstrated that the asparagine of the SNSL motif is essential in this inhibition. We prove for first time the existence of legumain inhibitors in plants. (c) 2007 Federation of European Biochemical Societies. Published by Elsevier B.V. All rights reserved.

L4 ANSWER 8 OF 63 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2007184455 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17350006
TITLE: Legumain/asparaginyl endopeptidase controls extracellular matrix remodeling through the degradation of fibronectin in mouse renal proximal tubular cells.
AUTHOR: Morita Yoshikata; Araki Hisazumi; Sugimoto Toshiro; Takeuchi Keisuke; Yamane Takuya; Maeda Toshinaga; Yamamoto Yoshio; Nishi Katsuji; Asano Masahide; Shirahama-Noda Kanae; Nishimura Mikio; Uzu Takashi; Hara-Nishimura Ikuko; Koya Daisuke; Kashiwagi Atsunori; Ohkubo Iwao
CORPORATE SOURCE: Department of Medical Biochemistry, Shiga University of Medical Science, Seta, Otsu 520-2192, Japan.
SOURCE: FEBS letters, (2007 Apr 3) Vol. 581, No. 7, pp. 1417-24. Electronic Publication: 2007-03-05. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200706
ENTRY DATE: Entered STN: 28 Mar 2007
Last Updated on STN: 7 Jun 2007
Entered Medline: 6 Jun 2007

AB Legumain/asparaginyl endopeptidase (EC 3.4.22.34) is a novel cysteine protease that is abundantly expressed in the late endosomes and lysosomes of renal proximal tubular cells. Recently, emerging evidence has indicated that legumain might play an important role in control of extracellular matrix turnover in various pathological conditions such as tumor growth/metastasis and progression of atherosclerosis. We initially found that purified legumain can directly degrade fibronectin, one of the main components of the extracellular matrix, in vitro. Therefore, we examined the effect of legumain on fibronectin degradation in cultured mouse renal proximal tubular cells. Fibronectin processing can be inhibited by chloroquine, an inhibitor of lysosomal degradation, and can be enhanced by the overexpression of legumain, indicating that fibronectin degradation occurs in the presence of legumain in lysosomes from renal proximal tubular cells. Furthermore, in legumain-deficient mice, unilateral ureteral obstruction (UUO)-induced renal interstitial protein accumulation of fibronectin and renal interstitial fibrosis were markedly enhanced. These findings indicate that legumain might have an important role in extracellular matrix remodeling via the degradation of fibronectin in renal proximal tubular cells.

L4 ANSWER 9 OF 63 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2007462862 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17681230
TITLE: Characterization of asparaginyl endopeptidase, legumain induced by blood feeding in the ixodid tick Haemaphysalis longicornis.
AUTHOR: Abdul Alim M; Tsuji Naotoshi; Miyoshi Takeharu; Khyrul Islam M; Huang Xiaohong; Motobu Maki; Fujisaki Kozo
CORPORATE SOURCE: Laboratory of Parasitic Diseases, National Institute of Animal Health, National Agricultural and Food Research Organization, Tsukuba, Ibaraki 305-0856, Japan.
SOURCE: Insect biochemistry and molecular biology, (2007 Sep) Vol. 37, No. 9, pp. 911-22. Electronic Publication: 2007-05-06. Journal code: 9207282. ISSN: 0965-1748.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB279705
ENTRY MONTH: 200712
ENTRY DATE: Entered STN: 8 Aug 2007
Last Updated on STN: 11 Dec 2007
Entered Medline: 6 Dec 2007

AB We characterize here a cDNA from the ixodid tick Haemaphysalis longicornis, which encodes an asparaginyl endopeptidase , legumain (HlLgm), that was present as a functional molecule in the midgut of this tick. Endogenous HlLgm was detected as a 38-kDa antigen in H. longicornis extracts and was seen throughout all developmental stages. Endogenous HlLgm was mainly localized in the midgut epithelium by immunohistochemistry, and was shown to be up-regulated by the host blood-feeding process. Recombinant HlLgm (rHlLgm) produced in Escherichia coli was shown to hydrolyze the synthetic substrate Z-Ala-Ala-Asn-MCA at the rate of 6.42x10(-4)mumol/min/mg protein. Its activity was inhibited by the thiol blocking reagents iodoacetamide and N-ethylmaleimide. The enzyme was shown to possess a unique feature of having an autocatalyzed cleavage at asparagines(364-365) at the C-terminus of both endogenous HlLgm and rHlLgm. rHlLgm degraded bovine hemoglobin and bovine serum albumin (BSA) showing its strict specificity for hydrolysis of the peptide on the carboxyl side of the asparagines, as demonstrated by internal amino acid sequence analysis of proteolytic product of BSA cleavage. These results suggest that HlLgm plays an important role in host blood-meal digestion and may be critical for the final process of digestion of blood components.

L4 ANSWER 10 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2007:567760 SCISEARCH
THE GENUINE ARTICLE: 159NS
TITLE: Presentation of the Goodpasture autoantigen requires proteolytic unlocking steps that destroy prominent T cell epitopes
AUTHOR: Phelps, Richard. G. (Reprint)
CORPORATE SOURCE: Univ Edinburgh, MRC, Ctr Inflammat Res Renal Autoimmunity, Queens Med Res Inst, 47 Little France Crescent, Edinburgh EH16 4TJ, Midlothian, Scotland (Reprint)
AUTHOR: Zou, Juan; Henderson, Lorna; Thomas, Vicky; Swan, Patricia; Turner, A. Neil
CORPORATE SOURCE: Univ Edinburgh, MRC, Ctr Inflammat Res Renal Autoimmunity, Queens Med Res Inst, Edinburgh EH16 4TJ, Midlothian, Scotland
E-mail: richard.phelps@ed.ac.uk
COUNTRY OF AUTHOR: Scotland
SOURCE: JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, (MAR 2007) Vol. 18, No. 3, pp. 771-779.
ISSN: 1046-6673.
PUBLISHER: AMERICAN SOCIETY NEPHROLOGY, 1725 I ST, NW STE 510, WASHINGTON, DC 20006 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 26
ENTRY DATE: Entered STN: 14 Jun 2007
Last Updated on STN: 14 Jun 2007
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The most abundant autoreactive T cells in patients with Goodpasture's disease are specific for peptides in the autoantigen that have high affinity for the disease-associated HLA class II molecule, DR15. How can such T cells escape self-tolerance mechanisms? This study showed that

these peptides are highly susceptible to destruction in the earliest stages of antigen processing, and some must be cleaved for antigen digestion to be possible ("unlocking"). Goodpasture autoantigen [collagen alpha 3(IV)NC1; approximatelv 31 kD] that was incubated with B cell lysosomes was cleaved within a few minutes to form approximately 9- and approximately 22-kD fragments, then increasing quantities of smaller peptides. The processing was completely abrogated by pepstatin A, a specific inhibitor of cathepsin D/E, even though lysosomal extracts contain a rich array of proteases. Purified cathepsin D generated the same major alpha 3(IV)NC1 fragments as entire lysosomes, suggesting that cathepsin D cleavages are required to initiate alpha 3(IV)NC1 processing. The initial unlocking cleavages destroyed two major self-epitopes, and subsequent preferred cleavages destroyed all of the other T cell epitopes that are recognized by most patients' autoreactive T cells. The responses of T cell clones that are specific for a major disease-associated peptide to antigen-pulsed intact antigen-presenting cells were substantially enhanced by pepstatin A treatment. Therefore, cathepsin D activity significantly diminishes presentation of alpha 3(IV)NC1 peptides that are recognized by patients' T cells by destroying the peptides in early processing. These observations can explain why the mature T cell repertoire includes reactivity toward these self-peptides and suggests that a key factor in disease initiation is likely to be a shift in antigen processing.

L4 ANSWER 11 OF 63 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2007262337 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17336985
TITLE: IrAE: an asparaginyl endopeptidase (legumain) in the gut of the hard tick Ixodes ricinus.
AUTHOR: Sojka Daniel; Hajdusek Ondrej; Dvorak Jan; Sajid Mohammed; Franta Zdenek; Schneider Eric L; Craik Charles S; Vancova Marie; Buresova Veronika; Bogyo Matthew; Sexton Kelly B; McKerrow James H; Caffrey Conor R; Kopacek Petr
CORPORATE SOURCE: Institute of Parasitology, Biology Centre of the Academy of Sciences of the Czech Republic and Faculty of Biological Sciences, University of South Bohemia, Ceske Budejovice, Czech Republic.
CONTRACT NUMBER: T32 CA108462-02 (United States NCI NIH HHS)
SOURCE: International journal for parasitology, (2007 Jun) Vol. 37, No. 7, pp. 713-24. Electronic Publication: 2007-01-30. Journal code: 0314024. ISSN: 0020-7519. Report No.: NLM-NIHMS65920; NLM-PMC2587490.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AY584752
ENTRY MONTH: 200801
ENTRY DATE: Entered STN: 3 May 2007 Last Updated on STN: 9 Jan 2008 Entered Medline: 8 Jan 2008

AB Ticks are ectoparasitic blood-feeders and important vectors for pathogens including arboviruses, rickettsiae, spirochetes and protozoa. As obligate blood-feeders, one possible strategy to retard disease transmission is disruption of the parasite's ability to digest host proteins. However, the constituent peptidases in the parasite gut and their potential interplay in the digestion of the blood meal are poorly understood. We have characterised a novel asparaginyl endopeptidase (legumain) from the hard tick Ixodes ricinus (termed IrAE), which we believe is the first such characterisation of a clan CD family C13

cysteine peptidase (protease) in arthropods. By RT-PCR of different tissues, IrAE mRNA was only expressed in the tick gut. Indirect immunofluorescence and EM localised IrAE in the digestive vesicles of gut cells and within the peritrophic matrix. IrAE was functionally expressed in Pichia pastoris and reacted with a specific peptidyl fluorogenic substrate, and acyloxymethyl ketone and aza-asparagine Michael acceptor inhibitors. IrAE activity was unstable at pH > or = 6.0 and was shown to have a strict specificity for asparagine at P1 using a positional scanning synthetic combinatorial library. The enzyme hydrolyzed protein substrates with a pH optimum of 4.5, consistent with the pH of gut cell digestive vesicles. Thus, IrAE cleaved the major protein of the blood meal, hemoglobin, to a predominant peptide of 4kDa. Also, IrAE trans-processed and activated the zymogen form of Schistosoma mansoni cathepsin B1 -- an enzyme contributing to hemoglobin digestion in the gut of that bloodfluke. The possible functions of IrAE in the gut digestive processes of I. ricinus are compared with those suggested for other hematophagous parasites.

L4 ANSWER 12 OF 63 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2007037567 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17189693
TITLE: Design of cell-permeable, fluorescent activity-based probes for the lysosomal cysteine protease asparaginyl endopeptidase (AEP)/legumain.
AUTHOR: Sexton Kelly B; Witte Martin D; Blum Galia; Bogyo Matthew
CORPORATE SOURCE: Department of Pathology, Stanford University School of Medicine, 300 Pasteur Dr., Stanford, CA 940305, USA.
CONTRACT NUMBER: R01 EB005011-02 (United States NIBIB)
R01-EB005011 (United States NIBIB)
U54 RR020843 (United States NCRR)
U54 RR020843-028126 (United States NCRR)
SOURCE: Bioorganic & medicinal chemistry letters, (2007 Feb 1) Vol. 17, No. 3, pp. 649-53. Electronic Publication: 2006-11-06. Journal code: 9107377. ISSN: 0960-894X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200704
ENTRY DATE: Entered STN: 23 Jan 2007
Last Updated on STN: 4 Apr 2007
Entered Medline: 3 Apr 2007
AB Asparaginyl endopeptidase (AEP), also known as legumain, is a cysteine protease that has been ascribed roles in antigen presentation yet its exact role in human biology remains poorly understood. We report here, the use of a positional scanning combinatorial library of peptide AOMKs containing a P1 aspartic acid to probe the P2, P3, and P4 subsite specificity of endogenous legumain. Using inhibitor specificity profiles of cathepsin B and legumain, we designed fluorescent ABPs that are highly selective, cell-permeable reagents for monitoring legumain activity in complex proteomes.

L4 ANSWER 13 OF 63 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2006732192 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16874311
TITLE: Colocalization of cystatin M/E and cathepsin V in lamellar granules and corneodesmosomes suggests a functional role in epidermal differentiation.

AUTHOR: Zeeuwen Patrick L J M; Ishida-Yamamoto Akemi; van Vlijmen-Willems Ivonne M J J; Cheng Tsing; Bergers Mieke; Iizuka Hajime; Schalkwijk Joost
CORPORATE SOURCE: Department of Dermatology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.. p.zeeuwen@derma.umcn.nl
SOURCE: The Journal of investigative dermatology, (2007 Jan) Vol. 127, No. 1, pp. 120-8. Electronic Publication: 2006-07-27. Journal code: 0426720. E-ISSN: 1523-1747.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200701
ENTRY DATE: Entered STN: 19 Dec 2006
Last Updated on STN: 4 Jan 2007
Entered Medline: 3 Jan 2007

AB Cystatin M/E is a cysteine protease inhibitor with two distinct binding sites for papain-like cysteine proteases (family C1) and the asparaginyl endopeptidase (AEP) legumain of family C13. We have previously demonstrated that deficiency of cystatin M/E in mice causes ichthyosiform skin changes and barrier disruption, which could be caused by unrestrained AEP activity. Recently, we provided biochemical evidence that human cathepsin V (CTSV) and cathepsin L (CTSL) are additional biological targets for human cystatin M/E. To address the possible role of these three proteases and their inhibitor in epidermal differentiation, we investigated the localization of these proteins in normal human skin. Whereas CTSL and AEP were broadly expressed in epithelial cells of the skin, we found a specific colocalization of cystatin M/E and CTSV in the stratum granulosum and in the root sheets of the hair follicle, using immunofluorescence microscopy. Immunoelectron microscopy revealed that cystatin M/E and CTSV are separately transported within the lamellar granules. Cystatin M/E was also found in the extracellular space in the stratum corneum associated with corneodesmosomes, where it was closely associated with CTSV. Based on the striking stratum-specific colocalization of cystatin M/E and CTSV, we propose that these molecules could have an important role in epidermal differentiation and desquamation.

L4 ANSWER 14 OF 63 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2006735702 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17028179
TITLE: A multienzyme network functions in intestinal protein digestion by a platyhelminth parasite.
AUTHOR: Delcroix Melaine; Sajid Mohammed; Caffrey Conor R; Lim Kee-C; Dvorak Jan; Hsieh Ivy; Bahgat Mahmoud; Dissous Colette; McKerrow James H
CORPORATE SOURCE: Department of Pathology, Tropical Disease Research Unit and Sandler Center for Basic Research in Parasitic Diseases, University of California, San Francisco, California 94158, USA.. jmck@cgl.ucsf.edu
CONTRACT NUMBER: AI-053247 (United States NIAID)
SOURCE: The Journal of biological chemistry, (2006 Dec 22) Vol. 281, No. 51, pp. 39316-29. Electronic Publication: 2006-10-06. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200702
ENTRY DATE: Entered STN: 19 Dec 2006
Last Updated on STN: 7 Feb 2007
Entered Medline: 6 Feb 2007

AB Proteases frequently function not only as individual enzymes but also in cascades or networks. A notable evolutionary switch occurred in one such protease network that is involved in protein digestion in the intestine. In vertebrates, this is largely the work of trypsin family serine proteases, whereas in invertebrates, cysteine proteases of the papain family and aspartic proteases assume the role. Utilizing a combination of protease class-specific inhibitors and RNA interference, we deconvoluted such a network of major endopeptidases functioning in invertebrate intestinal protein digestion, using the parasitic helminth, Schistosoma mansoni as an experimental model. We show that initial degradation of host blood proteins is ordered, occasionally redundant, and substrate-specific. Although inhibition of parasite cathepsin D had a greater effect on primary cleavage of hemoglobin, inhibition of cathepsin B predominated in albumin degradation. Nevertheless, in both cases, inhibitor combinations were synergistic. An asparaginyl endopeptidase (legumain) also synergized with cathepsin B and L in protein digestion, either by zymogen activation or facilitating substrate cleavage. This protease network operates optimally in acidic pH compartments either in the gut lumen or in vacuoles of the intestinal lining cells. Defining the role of each of these major enzymes now provides a clearer understanding of the function of a complex protease network that is conserved throughout invertebrate evolution. It also provides insights into which of these proteases are logical targets for development of chemotherapy for schistosomiasis, a major global health problem.

L4 ANSWER 15 OF 63 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2006352183 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16601115
TITLE: Structural basis of reduction-dependent activation of human cystatin F.
AUTHOR: Schuttelkopf Alexander W; Hamilton Garth; Watts Colin; van Aalten Daan M F
CORPORATE SOURCE: Division of Biological Chemistry and Molecular Microbiology, Wellcome Trust Biocentre, School of Life Sciences, University of Dundee, Dow Street, Dundee DD1 5EH, Scotland.
SOURCE: The Journal of biological chemistry, (2006 Jun 16) Vol. 281, No. 24, pp. 16570-5. Electronic Publication: 2006-04-06.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-2CH9
ENTRY MONTH: 200608
ENTRY DATE: Entered STN: 13 Jun 2006
Last Updated on STN: 2 Aug 2006
Entered Medline: 1 Aug 2006

AB Cystatins are important natural cysteine protease inhibitors targeting primarily papain-like cysteine proteases, including cathepsins and parasitic proteases like cruzipain, but also mammalian asparaginyl endopeptidase. Mammalian cystatin F, which is expressed almost exclusively in hematopoietic cells and accumulates in lysosome-like organelles, has been implicated in the regulation of antigen

presentation and other immune processes. It is an unusual cystatin superfamily member with a redox-regulated activation mechanism and a restricted specificity profile. We describe the 2.1A crystal structure of human cystatin F in its dimeric "off" state. The two monomers interact in a fashion not seen before for cystatins or cystatin-like proteins that is crucially dependent on an unusual intermolecular disulfide bridge, suggesting how reduction leads to monomer formation and activation. Strikingly, core sugars for one of the two N-linked glycosylation sites of cystatin F are well ordered, and their conformation and interactions with the protein indicate that this unique feature of cystatin F may modulate its inhibitory properties, in particular its reduced affinity toward asparaginyl endopeptidase compared with other cystatins.

L4 ANSWER 16 OF 63 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 2006331066 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16565075
TITLE: Cystatin M/E is a high affinity inhibitor of cathepsin V and cathepsin L by a reactive site that is distinct from the legumain-binding site. A novel clue for the role of cystatin M/E in epidermal cornification.
AUTHOR: Cheng Tsing; Hitomi Kiyotaka; van Vlijmen-Willems Ivonne M J J; de Jongh Gys J; Yamamoto Kanae; Nishi Koji; Watts Colin; Reinheckel Thomas; Schalkwijk Joost; Zeeuwen Patrick L J M
CORPORATE SOURCE: Department of Dermatology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, P. O. Box 9101, 6500 HB Nijmegen, The Netherlands.
SOURCE: The Journal of biological chemistry, (2006 Jun 9) Vol. 281, No. 23, pp. 15893-9. Electronic Publication: 2006-03-24. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200608
ENTRY DATE: Entered STN: 6 Jun 2006
Last Updated on STN: 24 Aug 2006
Entered Medline: 23 Aug 2006

AB Cystatin M/E is a high affinity inhibitor of the asparaginyl endopeptidase legumain, and we have previously reported that both proteins are likely to be involved in the regulation of stratum corneum formation in skin. Although cystatin M/E contains a predicted binding site for papain-like cysteine proteases, no high affinity binding for any member of this family has been demonstrated so far. We report that human cathepsin V (CTSV) and human cathepsin L (CTSL) are strongly inhibited by human cystatin M/E. Kinetic studies show that Ki values of cystatin M/E for the interaction with CTSV and CTSL are 0.47 and 1.78 nM, respectively. On the basis of the analogous sites in cystatin C, we used site-directed mutagenesis to identify the binding sites of these proteases in cystatin M/E. We found that the W135A mutant was rendered inactive against CTSV and CTSL but retained legumain-inhibiting activity. Conversely, the N64A mutant lost legumain-inhibiting activity but remained active against the papain-like cysteine proteases. We conclude that legumain and papain-like cysteine proteases are inhibited by two distinct non-overlapping sites. Using immunohistochemistry on normal human skin, we found that cystatin M/E co-localizes with CTSV and CTSL. In addition, we show that CTSL is the elusive enzyme that processes and activates epidermal transglutaminase 3. The identification of CTSV and CTSL as novel targets for cystatin M/E, their (co)-expression in the stratum

granulosum of human skin, and the activity of CTSL toward transglutaminase 3 strongly imply an important role for these enzymes in the differentiation process of human epidermis.

L4 ANSWER 17 OF 63 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2006369998 EMBASE
TITLE: Targeting tumor-associated macrophages as a novel strategy against breast cancer.
AUTHOR: Luo, Yunping; Zhou, He; Krueger, Jorg; Kaplan, Charles; Lee, Sung-Hyung; Dolman, Carrie; Markowitz, Dorothy; Wu, Wenyuan; Liu, Cheng; Reisfeld, Ralph A.; Xiang, Rong (correspondence)
CORPORATE SOURCE: Department of Immunology, Scripps Research Institute, San Diego, CA, United States. rxiang@scripps.edu
AUTHOR: Luo, Yunping
CORPORATE SOURCE: Key Laboratory of Laboratory Medical Diagnostics, Ministry of Education, Chongqing University of Medical Sciences, Chongqing, China.
AUTHOR: Xiang, Rong (correspondence)
CORPORATE SOURCE: Scripps Research Institute, R218, IMM13, 10550 North Torrey Pines Road, San Diego, CA 92037, United States. rxiang@scripps.edu
SOURCE: Journal of Clinical Investigation, (1 Aug 2006) Vol. 116, No. 8, pp. 2132-2141.
Refs: 46
ISSN: 0021-9738 E-ISSN: 1558-8238 CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 22 Aug 2006
Last Updated on STN: 22 Aug 2006

AB Tumor-associated macrophages (TAMs) are associated with tumor progression and metastasis. Here, we demonstrate for the first time that legumain, a member of the asparaginyl endopeptidase family functioning as a stress protein, overexpressed by TAMs, provides an ideal target molecule. In fact, a legumain-based DNA vaccine served as a tool to prove this point, as it induced a robust CD8(+) T cell response against TAMs, which dramatically reduced their density in tumor tissues and resulted in a marked decrease in proangiogenic factors released by TAMs such as TGF-β, TNF-α, MMP-9, and VEGF. This, in turn, led to a suppression of both tumor angiogenesis and tumor growth and metastasis. Importantly, the success of this strategy was demonstrated in murine models of metastatic breast, colon, and non-small cell lung cancers, where 75% of vaccinated mice survived lethal tumor cell challenges and 62% were completely free of metastases. In conclusion, decreasing the number of TAMs in the tumor stroma effectively altered the tumor microenvironment involved in tumor angiogenesis and progression to markedly suppress tumor growth and metastasis. Gaining better insights into the mechanisms required for an effective intervention in tumor growth and metastasis may ultimately lead to new therapeutic targets and better anticancer strategies.

L4 ANSWER 18 OF 63 MEDLINE on STN DUPLICATE 13

ACCESSION NUMBER: 2006694729 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17132111
TITLE: Two secreted cystatins of the soft tick Ornithodoros moubata: differential expression pattern and inhibitory specificity.

AUTHOR: Grunclova Lenka; Horn Martin; Vancova Marie; Sojka Daniel; Franta Zdenek; Mares Michael; Kopacek Petr
CORPORATE SOURCE: Faculty of Biological Sciences, University of South Bohemia, CZ-370 05 Ceske Budejovice, Czech Republic.
SOURCE: Biological chemistry, (2006 Dec) Vol. 387, No. 12, pp. 1635-44.
Journal code: 9700112. ISSN: 1431-6730.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200701
ENTRY DATE: Entered STN: 30 Nov 2006
Last Updated on STN: 25 Jan 2007
Entered Medline: 24 Jan 2007

AB Two genes coding for cysteine peptidase inhibitors of the cystatin family (Om-cystatin 1 and 2) were isolated from a gut-specific cDNA library of the soft tick Ornithodoros moubata. Both cystatins were clearly down-regulated after a blood meal. Om-cystatin 1 is mainly expressed in the tick gut, while Om-cystatin 2 mRNA was also found in other tick tissues. Authentic Om-cystatin 2 was significantly more abundant than Om-cystatin 1 in the gut contents of fasting ticks and was associated with hemosome-derived residual bodies accumulated in the gut lumen. Om-cystatin 2 was also expressed by type 2 secretory cells in the salivary glands of unfed ticks. The inhibitory specificity of recombinant Om-cystatins 1 and 2 was tested with mammalian cysteine peptidases, as well as endogenous cysteine peptidases present in the tick gut. Both cystatins efficiently inhibited papain-like peptidases, including cathepsin B and H, but differed significantly in their affinity towards cathepsin C and failed to block asparaginyl endopeptidase. Our results suggest that the secreted cystatin isoinhibitors are involved in the regulation of multiple proteolytic targets in the tick digestive system and tick-host interaction.

L4 ANSWER 19 OF 63 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 2006097680 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16485008
TITLE: Peptidomic analysis of breast cancer reveals a putative surrogate marker for estrogen receptor-negative carcinomas.
AUTHOR: Traub Frank; Jost Marco; Hess Rudiger; Schorn Karl; Menzel Christoph; Budde Petra; Schulz-Knappe Peter; Lamping Norbert; Pich Andreas; Kreipe Hans; Tammen Harald
CORPORATE SOURCE: Institute of Pathology, Medizinische Hochschule Hannover, Hannover, Germany.
SOURCE: Laboratory investigation; a journal of technical methods and pathology, (2006 Mar) Vol. 86, No. 3, pp. 246-53.
Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200605
ENTRY DATE: Entered STN: 18 Feb 2006
Last Updated on STN: 19 May 2006
Entered Medline: 18 May 2006

AB Estrogen-receptor status provides a major biomarker in breast cancer classification and has an important impact on prognosis and treatment options. The aim of this study was to investigate peptide profiles of invasive breast cancer with positive (n=39) and negative receptor status (n=41). Peptide profiles were generated by 'Differential Peptide

Display', which is an offline-coupled combination of reversed-phase-HPLC and MALDI mass spectrometry. Mass spectrometric data were correlated with the immunohistochemically determined receptor state. Identification of peptides of interest was carried out by additional mass spectrometric methods (eg MALDI-TOF-TOF-MS-MS). Approximately 3000-7000 signals were detected per sample and thymosin alpha-1, an asparaginyl endopeptidase generated cleavage product of the ubiquitous acidic protein prothymosin-alpha, was found to differentiate the tumor samples according to their receptor status with the highest specificity. The concentration of Thymosin alpha-1 was found to be upregulated (n=37) in estrogen-negative cancer samples and downregulated (n=32) in estrogen-positive breast cancer samples. The expression of the precursor protein (Prothymosin-alpha) has been discussed previously as a prognostic factor in breast cancer. It is involved in the ER signal transduction pathway as an anti-coactivator-inhibitor. From our findings we conclude that Thymosin alpha-1 could serve as a surrogate marker in breast cancers and may indicate ER functionality.

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ACCESSION NUMBER: 2006:921460 SCISEARCH
THE GENUINE ARTICLE: 084YP
TITLE: Characterization of cysteine proteases in Malian medicinal plants
AUTHOR: Johansen H T (Reprint)
CORPORATE SOURCE: Univ Oslo, Sch Pharm, Dept Pharmaceut Biosci, POB 1068 Blindern, N-0316 Oslo, Norway (Reprint)
AUTHOR: Bah S; Paulsen B S; Diallo D
CORPORATE SOURCE: Univ Oslo, Sch Pharm, Dept Pharmaceut Biosci, N-0316 Oslo, Norway; Univ Oslo, Sch Pharm, Dept Pharmaceut Chem, N-0316 Oslo, Norway; Inst Natl Rech Sante Publ, Dept Med Tradit, Bamako, Mali
E-mail: h.t.johansen@farmasi.uio.no
COUNTRY OF AUTHOR: Norway; Mali
SOURCE: JOURNAL OF ETHNOPHARMACOLOGY, (19 SEP 2006) Vol. 107, No. 2, pp. 189-198.
ISSN: 0378-8741.
PUBLISHER: ELSEVIER IRELAND LTD, ELSEVIER HOUSE, BROOKVALE PLAZA, EAST PARK SHANNON, CO, CLARE, 00000, IRELAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41
ENTRY DATE: Entered STN: 5 Oct 2006
Last Updated on STN: 5 Oct 2006

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Extracts form 10 different Malian medicinal plants with a traditional use against schistosomiasis were investigated for their possible content of proteolytic activity. The proteolytic activity was studied by measuring the hydrolysis of two synthetic peptide substrates Z-Ala-Ala-Asn-NHMec and Z-Phe-Arg-NHMec. Legumain- and papain-like activities were found in all tested crude extracts except those from Entada africana, with the papain-like activity being the strongest. Cissus quadrangularis, Securidaca longepedunculata and Stylosanthes erecta extracts showed high proteolytic activities towards both substrates. After gel filtration the proteolytic activity towards the substrate Z-Ala-Ala-Asn-NHMec in root extract of Securidaca longepedunculata appeared to have Mr of 30 and 97 kDa, while the activity in extracts from Cissus quadrangularis was at 39 kDa. Enzymatic activity cleaving the substrate Z-Phe-Arg-NHMec showed apparent Mr of 97 and 26 kDa in extracts from roots and leaves of Securidaca longepedunculata, while in Cissus quadrangularis extracts the activity eluted at 39 and 20 kDa, with the highest activity in the latter. All Z-Phe-Arg-NHMec activities were

inhibited by E-64 but unaffected by PMSF The legumain activity was unaffected by E-64 and PMSF. The SDS-PAGE analysis exhibited five distinct gelatinolytic bands for Cissus quadrangularis extracts (115, 59, 31, 22 and 20 kDa), while two bands (59 and 30 kDa) were detected in Securidaca longepedunculata extracts. The inhibition profile of the gelatinolytic bands and that of the hydrolysis of the synthetic substrates indicate the cysteine protease class of the proteolytic activities. Several cysteine protease activities with different molecular weights along with a strong variability of these activities between species as well as between plant parts from the same species were observed. (c) 2006 Elsevier Ireland Ltd. All rights reserved.

L4 ANSWER 21 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:954139 SCISEARCH
THE GENUINE ARTICLE: 963HM
TITLE: Discovery, structural determination, and putative processing of the precursor protein that produces the cyclic trypsin inhibitor sunflower trypsin inhibitor 1
AUTHOR: Craik D J (Reprint)
CORPORATE SOURCE: Univ Queensland, Inst Mol Biosci, Asutralian Res Council, Ctr Funct & Appl Genom, Brisbane, Qld 4072, Australia (Reprint)
AUTHOR: Mulvenna J P; Foley F M
CORPORATE SOURCE: E-mail: d.craik@imb.uq.edu.au
COUNTRY OF AUTHOR: Australia
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (16 SEP 2005) Vol. 280, No. 37, pp. 32245-32253. ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 45
ENTRY DATE: Entered STN: 29 Sep 2005
Last Updated on STN: 29 Sep 2005

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Backbone-cyclized proteins are becoming increasingly well known, although the mechanism by which they are processed from linear precursors is poorly understood. In this report the sequence and structure of the linear precursor of a cyclic trypsin inhibitor, sunflower trypsin inhibitor 1 (SFTI-1) from sunflower seeds, is described. The structure indicates that the major elements of the reactive site loop of SFTI-1 are present before processing. This may have importance for a protease-mediated cyclizing reaction as the rigidity of SFTI-1 may drive the equilibrium of the reaction catalyzed by proteolytic enzymes toward the formation of a peptide bond rather than the normal cleavage reaction. The occurrence of residues in the SFTI-1 precursor susceptible to cleavage by asparaginyl proteases strengthens theories that involve this enzyme in the processing of SFTI-1 and further implicates it in the processing of another family of plant cyclic proteins, the cyclotides. The precursor reported here also indicates that despite strong active site sequence homology, SFTI-1 has no other similarities with the Bowman-Birk trypsin inhibitors, presenting interesting evolutionary questions.

L4 ANSWER 22 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:487445 SCISEARCH
THE GENUINE ARTICLE: 922AH
TITLE: Crystal structure of human cystatin D, a cysteine peptidase inhibitor with restricted

inhibition profile
AUTHOR: Abrahamson M (Reprint)
CORPORATE SOURCE: Lund Univ, Dept Clin Chem, Inst Lab Med, SE-22185 Lund, Sweden (Reprint)
AUTHOR: Alvarez-Fernandez M; Liang Y H; Su X D
CORPORATE SOURCE: Peking Univ, Natl Lab Prot Engn & Plant Genet Engn, Beijing 100871, Peoples R China; Ctr Chem & Chem Engn, Dept Mol Biophys, SE-22100 Lund, Sweden
E-mail: Magnus.Abrahamson@klinkem.lu.se; su-xd@pku.edu.cn
COUNTRY OF AUTHOR: Sweden; Peoples R China
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (6 MAY 2005) Vol. 280, No. 18, pp. 18221-18228.
ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 53
ENTRY DATE: Entered STN: 22 May 2005
Last Updated on STN: 18 Sep 2008
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cystatins are natural inhibitors of papain-like (family C1) and legumain-related (family C13) cysteine peptidases. Cystatin D is a type 2 cystatin, a secreted inhibitor found in human saliva and tear fluid. Compared with its homologues, cystatin D presents an unusual inhibition profile with a preferential inhibition cathepsin S > cathepsin H > cathepsin L and no inhibition of cathepsin B or pig legumain. To elucidate the structural reasons for this specificity, we have crystallized recombinant human Arg(26)-cystatin D and solved its structures at room temperature and at cryo conditions to 2.5- and 1.8-angstrom resolution, respectively. Human cystatin D presents the typical cystatin fold, with a five-stranded anti-parallel beta-sheet wrapped around a five-turn alpha-helix. The structures reveal differences in the peptidase-interacting regions when compared with other cystatins, providing plausible explanations for the restricted inhibitory specificity of cystatin D for some papain-like peptidases and its lack of reactivity toward legumain-related enzymes.

L4 ANSWER 23 OF 63 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 2005682163 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16188875
TITLE: In vitro proteolysis of phosphoenolpyruvate carboxylase from developing castor oil seeds by an endogenous thiol endopeptidase.
AUTHOR: Crowley Valerie; Gennidakis Sam; Plaxton William C
CORPORATE SOURCE: Department of Biology, Queen's University, Kingston, Ontario, Canada.
SOURCE: Plant & cell physiology, (2005 Nov) Vol. 46, No. 11, pp. 1855-62. Electronic Publication: 2005-09-27.
Journal code: 9430925. ISSN: 0032-0781.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200601
ENTRY DATE: Entered STN: 23 Dec 2005
Last Updated on STN: 25 Jan 2006
Entered Medline: 24 Jan 2006

AB Two novel phosphoenolpyruvate carboxylase (PEPC) isoforms have been biochemically characterized from endosperm of developing castor oil seeds (COS). The association of a 107 kDa PEPC subunit (p107) with an

immunologically unrelated bacterial PEPC-type 64 kDa polypeptide leads to marked physical and kinetic differences between the PEPC1 p107 homotetramer and PEPC2 p107/p64 heterooctamer. COS p107 is quite susceptible to limited proteolysis during PEPC purification. An endogenous asparaginyl endopeptidase appears to catalyze the in vitro cleavage of an approximately 120 amino acid polypeptide from the N-terminal end of p107, producing a truncated 98 kDa polypeptide (p98). Immunoblotting was used to estimate proteolytic activity by following the disappearance of p107 and concomitant appearance of p98 during incubation of clarified COS extracts at 4 degrees C. The in vitro proteolysis of p107 to p98 only occurred in the combined presence of 2 mM dithiothreitol and high salt concentrations (particularly SO(4) (2-) and PO(4) (2-) salts). Although p107-degrading activity was present throughout COS development, it was most pronounced in endosperm extracts from older beans. Several protease inhibitors, including two commercially available protease inhibitor cocktails, were tested for their ability to prevent p107 proteolysis. All of the inhibitors were ineffective except for 2,2'-dipyridyl disulfide (DPDS), a relatively inexpensive and underutilized active site inhibitor of plant thiol proteases. Asparaginyl endopeptidase activity of COS extracts was unaffected by 20% (NH(4))(2)SO(4) when determined in the presence or absence of 2 mM dithiothreitol using a spectrophotometric assay based upon the hydrolysis of benzoyl-L-Asn-p-nitroanilide. Thus, we propose that the combined presence of 2 mM dithiothreitol and 20% (NH(4))(2)SO(4) promotes a p107 conformational change that exposes the N-terminal region asparaginyl residue where p107 hydrolysis is believed to occur.

L4 ANSWER 24 OF 63 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005293944 EMBASE

TITLE: Multiple cathepsin B isoforms in schistosomula of Trichobilharzia regenti: Identification, characterisation and putative role in migration and nutrition.

AUTHOR: Dvorak, Jan; Sedinova, Miroslava; Mikes, Libor; Horak, Petr

CORPORATE SOURCE: Department of Parasitology, Faculty of Science, Charles University, Vinicna 7, CZ 12844 Prague, Czech Republic.

AUTHOR: Delcroix, Melaine; Sajid, Mohammed; McKerrow, James H.; Caffrey, Conor R. (correspondence)

CORPORATE SOURCE: Department of Pathology, Sandler Center for Basic Research in Parasitic Diseases, University of California San Francisco, San Francisco, CA 94143, United States. caffrey@cgl.ucsf.edu

AUTHOR: Rossi, Andrea; Sali, Andrej

CORPORATE SOURCE: Departments of Biopharmaceutical Sciences and Pharmaceutical Chemistry, California Institute for Quantitative Biomedical Research, University of California San Francisco, San Francisco, CA 94143, United States.

AUTHOR: Vopalensky, Vaclav; Pospisek, Martin

CORPORATE SOURCE: Department of Genetics and Microbiology, Faculty of Science, Charles University, Vinicna 5, CZ 12844 Prague, Czech Republic.

SOURCE: International Journal for Parasitology, (Jul 2005) Vol. 35, No. 8, pp. 895-910.
Refs: 43
ISSN: 0020-7519 CODEN: IJPYBT

PUBLISHER IDENT.: S 0020-7519(05)00100-1

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 037 Drug Literature Index
004 Microbiology: Bacteriology, Mycology, Parasitology and Virology

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 21 Jul 2005
Last Updated on STN: 21 Jul 2005

AB Among schistosomatids, Trichobilharzia regenti, displays an unusual migration through the peripheral and central nervous system prior to residence in the nasal cavity of the definitive avian host. Migration causes tissue degradation and neuromotor dysfunction both in birds and experimentally infected mice. Although schistosomula have a well-developed gut, the peptidases elaborated that might facilitate nutrition and migration are unknown. This is, in large part, due to the difficulty in isolating large numbers of migrating larvae. We have identified and characterised the major 33 kDa cathepsin B-like cysteine endopeptidase in extracts of migrating schistosomula using fluorogenic peptidyl substrates with high extinction coefficients and irreversible affinity-labels. From first strand schistosomula cDNA, degenerate PCR and Rapid Amplification of cDNA End protocols were used to identify peptidase isoforms termed TrCB1.1-TrCB1.6. Highest sequence homology is to the described Schistosoma mansoni and Schistosoma japonicum cathepsins B1. Two isoforms (TrCB1.5 and 1.6) encode putatively inactive enzymes as the catalytic cysteine is substituted by glycine. Two other isoforms, TrCB1.1 and 1.4, were functionally expressed as zymogens in Pichia pastoris. Specific polyclonal antibodies localised the peptidases exclusively in the gut of schistosomula and reacted with a 33 kDa protein in worm extracts. TrCB1.1 zymogen was unable to catalyse its own activation, but was trans-processed and activated by S. mansoni asparaginyl endopeptidase (SmAE aka. S. mansoni legumain). In contrast, TrCB1.4 zymogen auto-activated, but was resistant to the action of SmAE. Both activated isoforms displayed different pH-dependent specificity profiles with peptidyl substrates. Also, both isoforms degraded myelin basic protein, the major protein component of nervous tissue, but were inefficient against hemoglobin, thus supporting the adaptation of T. regenti gut peptidases to parasitism of host nervous tissue. .COPYRGT. 2005 Australian Society for Parasitology Inc. Published by Elsevier Ltd. All rights reserved.

L4 ANSWER 25 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:709440 SCISEARCH
THE GENUINE ARTICLE: 942VB
TITLE: Different cysteine proteinases involved in bone resorption and osteoclast formation
AUTHOR: Lerner U H (Reprint)
CORPORATE SOURCE: Umea Univ, Dept Oral Cell Biol, S-90187 Umea, Sweden (Reprint)
AUTHOR: Brage M; Abrahamson M; Lindstrom V; Grubb A
CORPORATE SOURCE: Lund Univ, Inst Lab Med, Dept Clin Chem, S-22185 Lund, Sweden
E-mail: ulf.lerner@odont.umu.se
COUNTRY OF AUTHOR: Sweden
SOURCE: CALCIFIED TISSUE INTERNATIONAL, (JUN 2005) Vol. 76, No. 6, pp. 439-447.
ISSN: 0171-967X.
PUBLISHER: SPRINGER, 233 SPRING STREET, NEW YORK, NY 10013 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 57
ENTRY DATE: Entered STN: 22 Jul 2005
Last Updated on STN: 20 Oct 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cysteine proteinases, especially cathepsin K, play an important role in osteoclastic degradation of bone matrix proteins and the process can,

consequently, be significantly inhibited by cysteine proteinase inhibitors. We have recently reported that cystatin C and other cysteine proteinase inhibitors also reduce osteoclast formation. However, it is not known which cysteine proteinase(s) are involved in osteoclast differentiation. In the present study, we compared the relative potencies of cystatins C and D as inhibitors of bone resorption in cultured mouse calvariae, osteoclastogenesis in mouse bone marrow cultures, and cathepsin K activity. Inhibition of cathepsin K activity was assessed by determining equilibrium constants for inhibitor complexes in fluorogenic substrate assays. The data demonstrate that whereas human cystatins C and D are equipotent as inhibitors of bone resorption, cystatin D is 10-fold less potent as an inhibitor of osteoclastogenesis and 200-fold less potent as an inhibitor of cathepsin K activity. A recombinant human cystatin C variant with Gly substitutions for residues Arg(8), Leu(9), Val(10), and Trp(106) did not inhibit bone resorption, had 1,000-fold decreased inhibitory effect on catbepsin K activity compared to wildtype cystatin C, but was equipotent with wildtype cystatin C as an inhibitor of osteoclastogenesis. It is concluded that (i) different cysteine proteinases are likely to be involved in bone resorption and osteoclast formation, (ii) cathepsin K may not be an exclusive target enzyme in any of the two systems, and (iii) the enzyme(s) involved in osteoclastogenesis might not be a typical papain-like cysteine proteinase.

L4 ANSWER 26 OF 63 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 2005038191 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15664654
TITLE: Bm-CPI-2, a cystatin from Brugia malayi nematode parasites, differs from Caenorhabditis elegans cystatins in a specific site mediating inhibition of the antigen-processing enzyme AEP.
AUTHOR: Murray Janice; Manoury Benedicte; Balic Adam; Watts Colin; Maizels Rick M
CORPORATE SOURCE: Institute of Immunology and Infection Research, Ashworth Laboratories, University of Edinburgh, West Mains Road, Scotland EH9 3JT, UK.
SOURCE: Molecular and biochemical parasitology, (2005 Feb) Vol. 139, No. 2, pp. 197-203.
Journal code: 8006324. ISSN: 0166-6851.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 25 Jan 2005
Last Updated on STN: 22 Apr 2005
Entered Medline: 21 Apr 2005

AB The filarial parasite Brugia malayi survives for many years in the human lymphatic system. One immune evasion mechanism employed by Brugia is thought to be the release of cysteine protease inhibitors (cystatins), and we have previously shown that the recombinant cystatin Bm-CPI-2 interferes with protease-dependent antigen processing in the MHC class II antigen presentation pathway. Analogy with vertebrate cystatins suggested that Bm-CPI-2 is bi-functional, with one face of the protein blocking papain-like proteases, and the other able to inhibit legumains such as asparaginyl endopeptidase (AEP). Site-directed mutagenesis was carried out on Bm-CPI-2 at Asn-77, the residue on which AEP inhibition is dependent in vertebrate homologues. Two mutations at this site (to Asp and Lys) showed 10-fold diminished and ablated activity respectively, in assays of AEP

inhibition, while blocking of papain-like proteases was reduced by only a small degree. Comparison of the B. malayi cystatins with two homologues encoded by the free-living model organism, Caenorhabditis elegans, suggested that while the papain site may be intact, the AEP site would not be functional. This supposition was tested with recombinant C. elegans proteins, Ce-CPI-1 (K08B4.6) and Ce-CPI-2 (R01B10.1), both of which block cathepsins and neither of which possess the ability to block AEP. Thus, Brugia CPI-2 may have convergently evolved to inhibit an enzyme important only in the mammalian environment.

L4 ANSWER 27 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:1050376 SCISEARCH
THE GENUINE ARTICLE: 974WC
TITLE: Activity-based probes that target diverse cysteine protease families
AUTHOR: Bogyo M (Reprint)
CORPORATE SOURCE: Stanford Univ, Sch Med, Dept Pathol, 300 Pasteur Dr, Stanford, CA 94030 USA (Reprint)
AUTHOR: Kato D; Boatright K M; Berger A B; Nazif T; Blum G; Ryan C; Chehade K A H; Salvesen G S
CORPORATE SOURCE: Stanford Univ, Sch Med, Dept Pathol, Stanford, CA 94030 USA; Stanford Univ, Sch Med, Canc Biol Grad Program, Stanford, CA 94030 USA; Burnham Inst, La Jolla, CA 92037 USA; Univ Calif San Francisco, Dept Biochem & Biophys, San Francisco, CA 94143 USA; Stanford Univ, Sch Med, Dept Microbiol & Immunol, Stanford, CA 94030 USA
E-mail: mbogyo@stanford.edu
COUNTRY OF AUTHOR: USA
SOURCE: NATURE CHEMICAL BIOLOGY, (JUN 2005) Vol. 1, No. 1, pp. 33-38.
ISSN: 1552-4450.
PUBLISHER: NATURE PUBLISHING GROUP, 345 PARK AVENUE SOUTH, NEW YORK, NY 10010-1707 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 28
ENTRY DATE: Entered STN: 28 Oct 2005
Last Updated on STN: 28 Oct 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Proteases are one of the largest and best-characterized families of enzymes in the human proteome. Unfortunately, the understanding of protease function in the context of complex proteolytic cascades remains in its infancy. One major reason for this gap in understanding is the lack of technologies that allow direct assessment of protease activity. We report here an optimized solid-phase synthesis protocol that allows rapid generation of activity-based probes (ABPs) targeting a range of cysteine protease families. These reagents selectively form covalent bonds with the active-site thiol of a cysteine protease, allowing direct biochemical profiling of protease activities in complex proteomes. We present a number of probes containing either a single amino acid or an extended peptide sequence that target caspases, legumains, gingipains and cathepsins. Biochemical studies using these reagents highlight their overall utility and provide insight into the biochemical functions of members of these protease families.

L4 ANSWER 28 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:1018873 SCISEARCH
THE GENUINE ARTICLE: 870QY
TITLE: VPE gamma exhibits a caspase-like activity that contributes to defense against pathogens

AUTHOR: Rojo E (Reprint)
CORPORATE SOURCE: Univ Calif Riverside, Ctr Plant Cell Biol, 2109 Batchelor Hall, Riverside, CA 92521 USA (Reprint)
AUTHOR: Martin R; Carter C; Zouhar J; Pan S Q; Plotnikova J; Jin H L; Paneque M; Sanchez-Serrano J J; Baker B; Ausubel F M; Raikhel N V
CORPORATE SOURCE: Univ Calif Riverside, Ctr Plant Cell Biol, Riverside, CA 92521 USA; Univ Calif Riverside, Dept Bot & Plant Sci, Riverside, CA 92521 USA; CSIC, Ctr Nacl Biotecnol, Dept Genet Mol Plantas, E-28049 Madrid, Spain; Harvard Univ, Sch Med, Dept Genet, Boston, MA 02114 USA; Massachusetts Gen Hosp, Dept Mol Biol, Boston, MA 02114 USA; USDA, Albany, CA 94710 USA; Univ Calif Berkeley, Ctr Plant Gene Express, Albany, CA 94710 USA
E-mail: erojo@cnb.uam.es; natasha.raikhel@ucr.edu
COUNTRY OF AUTHOR: USA; Spain
SOURCE: CURRENT BIOLOGY, (9 NOV 2004) Vol. 14, No. 21, pp. 1897-1906.
ISSN: 0960-9822.
PUBLISHER: CELL PRESS, 1100 MASSACHUSETTS AVE, CAMBRIDGE, MA 02138 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 35
ENTRY DATE: Entered STN: 16 Dec 2004
Last Updated on STN: 16 Dec 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Caspases are a family of aspartate-specific cysteine proteases that play an essential role in initiating and executing programmed cell death (PCD) in metazoans. Caspase-like activities have been shown to be required for the initiation of PCD in plants, but the genes encoding those activities have not been identified. VPEgamma, a cysteine protease, is induced during senescence, a form of PCD in plants, and is localized in precursor protease vesicles and vacuoles, compartments associated with PCD processes in plants.

Results: We show that VPEgamma binds in vivo to a general caspase inhibitor and to caspase-1-specific inhibitors, which block the activity of VPEgamma. A cysteine protease inhibitor, cystatin, accumulates to 20-fold higher levels in vpegamma mutants. Homologs of cystatin are known to suppress hypersensitive cell death in plant and animal systems. We also report that infection with an avirulent strain of Pseudomonas syringae results in an increase of caspase-1 activity, and this increase is partially suppressed in vpegamma mutants. Plants overexpressing VPEgamma exhibit a greater amount of ion leakage during infection with P. syringae, suggesting that VPEgamma may regulate cell death progression during plant-pathogen interaction. VPEgamma expression is induced after infection with P. syringae, Botrytis cinerea, and turnip mosaic virus, and knockout of VPEgamma results in increased susceptibility to these pathogens.

Conclusions: We conclude that VPEgamma is a caspase-like enzyme that has been recruited in plants to regulate vacuole-mediated cell dismantling during cell death, a process that has significant influence in the outcome of a diverse set of plant-pathogen interactions.

L4 ANSWER 29 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:361576 SCISEARCH
THE GENUINE ARTICLE: 809MZ
TITLE: Aza-peptide Michael acceptors: A new class of inhibitors specific for caspases and other clan CD cysteine proteases
AUTHOR: Powers J C (Reprint)

CORPORATE SOURCE: Georgia Inst Technol, Sch Chem & Biochem, Atlanta, GA 30332 USA (Reprint)
AUTHOR: Ekici O D; Gotz M G; James K E; Li Z Z; Rukamp B J; Asgian J L; Caffrey C R; Hansell E; Dvorak J; McKerrow J H; Potempa J; Travis J; Mikolajczyk J; Salvesen G S
CORPORATE SOURCE: Georgia Inst Technol, Parker H Petit Inst Bioengn & Biosci, Atlanta, GA 30332 USA; Univ Calif San Francisco, Sandler Ctr Basic Res Parasit Dis, San Francisco, CA 94143 USA; Charles Univ, Dept Parasitol, Fac Sci, CZ-12844 Prague 2, Czech Republic; Jagiellonian Univ, Fac Biotechnol, Krakow, Poland; Univ Georgia, Dept Biochem & Mol Biol, Athens, GA 30602 USA; Burnham Inst, Program Apoptosis & Cell Death Res, La Jolla, CA 92037 USA
E-mail: james.powers@chemistry.gatech.edu
COUNTRY OF AUTHOR: USA; Czech Republic; Poland
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (8 APR 2004) Vol. 47, No. 8, pp. 1889-1892.
ISSN: 0022-2623.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 23
ENTRY DATE: Entered STN: 30 Apr 2004
Last Updated on STN: 30 Apr 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Aza-peptide Michael acceptors are a new class of irreversible inhibitors that are highly potent and specific for clan CD cysteine proteases. The aza-Asp derivatives were specific for caspases, while aza-Asn derivatives were effective legumain inhibitors. Aza-Lys and aza-Orn derivatives were potent inhibitors of gingipain K and clostripain. Aza-peptide Michael acceptors showed no cross reactivity toward papain, cathepsin B, and calpain.

L4 ANSWER 30 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:432417 SCISEARCH
THE GENUINE ARTICLE: 816XN
TITLE: Evidence that unrestricted legumain activity is involved in disturbed epidermal cornification in cystatin M/E deficient mice
AUTHOR: Zeeuwen P L J M (Reprint)
CORPORATE SOURCE: Univ Med Ctr Nijmegen, Nijmegen Ctr Mol Life Sci, Dept Dermatol, POB 9101, NL-6500 HB Nijmegen, Netherlands (Reprint)
AUTHOR: van Vlijmen-Willems I M J J; Olthuis D; Johansen H T; Hitomi K; Hara-Nishimura I; Powers J C; James K E; op den Camp H J; Lemmens R; Schalkwijk J
CORPORATE SOURCE: Univ Med Ctr Nijmegen, Nijmegen Ctr Mol Life Sci, Dept Dermatol, NL-6500 HB Nijmegen, Netherlands; Dept Pharmacol, Sch Pharm, Oslo, Norway; Nagoya Univ, Grad Sch Bioagr Sci, Dept Appl Mol Biosci, Nagoya, Aichi, Japan; Kyoto Univ, Grad Sch Sci, Dept Bot, Kyoto, Japan; Georgia Inst Technol, Sch Chem & Biochem, Atlanta, GA 30332 USA; Univ Nijmegen, Fac Sci, Dept Microbiol, Nijmegen, Netherlands
COUNTRY OF AUTHOR: Netherlands; Norway; Japan; USA
SOURCE: HUMAN MOLECULAR GENETICS, (15 MAY 2004) Vol. 13, No. 10, pp. 1069-1079.
ISSN: 0964-6906.
PUBLISHER: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.

DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 56
ENTRY DATE: Entered STN: 28 May 2004
Last Updated on STN: 28 May 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Homozygosity for Cst6 null alleles causes the phenotype of the ichq mouse, which is a model for human harlequin ichthyosis (OMIM 242500), a genetically heterogeneous group of keratinization disorders. Here we report evidence for the mechanism by which deficiency of the cysteine protease inhibitor cystatin M/E (the Cst6 gene product) leads to disturbed cornification, impaired barrier function and dehydration. Absence of cystatin M/E causes unrestricted activity of its target protease legumain in hair follicles and epidermis, which is the exact location where cystatin M/E is normally expressed. Analysis of stratum corneum proteins revealed a strong decrease of soluble loricrin monomers in skin extracts of ichq mice, although normal levels of loricrin were present in the stratum granulosum and stratum corneum of ichq mice, as shown by immunohistochemistry. This suggested a premature or enhanced crosslinking of loricrin monomers in ichq mice by transglutaminase 3 (TGase 3). In these mice, we indeed found strongly increased levels of TGase 3 that was processed into its activated 30 and 47 kDa subunits, compared to wild-type mice. This study shows that cystatin M/E and legumain form a functional dyad in epidermis in vivo. Disturbance of this protease-antiprotease balance causes increased enzyme activity of TGase 3 that could explain the observed abnormal cornification.

L4 ANSWER 31 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:812767 SCISEARCH
THE GENUINE ARTICLE: 852RU
TITLE: Multifunctional role of plant cysteine proteinases
AUTHOR: Zagdanska B (Reprint)
CORPORATE SOURCE: Agr Univ Warsaw, Dept Biochem, Nowoursynowska 159, PL-02776 Warsaw, Poland (Reprint)
AUTHOR: Grudkowska M
CORPORATE SOURCE: Agr Univ Warsaw, Dept Biochem, PL-02776 Warsaw, Poland; Plant Breeding & Acclimatizat Inst, Plant Physiol & Biochem Dept, Warsaw, Poland
E-mail: zagdanska@delta.sggw.waw.pl
COUNTRY OF AUTHOR: Poland
SOURCE: ACTA BIOCHIMICA POLONICA, (2004) Vol. 51, No. 3, pp. 609-624.
ISSN: 0001-527X.
PUBLISHER: ACTA BIOCHIMICA POLONICA, PASTEURA 3, 02-093 WARSAW, POLAND.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 105
ENTRY DATE: Entered STN: 8 Oct 2004
Last Updated on STN: 8 Oct 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cysteine proteinases also referred to as thiol proteases play an essential role in plant growth and development but also in senescence and programmed cell death, in accumulation of storage proteins such as in seeds, but also in storage protein mobilization. Thus, they participate in both anabolic and catabolic processes. In addition, they are involved in signalling pathways and in the response to biotic and abiotic stresses. In this review an attempt was undertaken to illustrate these multiple roles of cysteine proteinases and the mechanisms underlying their action.

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STN
ACCESSION NUMBER: 2004:635029 SCISEARCH
THE GENUINE ARTICLE: 835QI
TITLE: Proteinases participating in the processing and activation of prolegumain in primary cultured rat macrophages
AUTHOR: Ishidoh K (Reprint)
CORPORATE SOURCE: Tokushima Bunri Univ, Inst Hlth Sci, Yamashiro Cho, Tokushima 7708514, Japan (Reprint)
AUTHOR: Lecaille F; Muno D; Kominami E
CORPORATE SOURCE: Juntendo Univ, Sch Med, Dept Biochem, Bunkyo Ku, Tokyo 1138421, Japan; Fac Med Tours, INSERM, U618, F-37032 Tours, France
E-mail: kishidoh@tokushima.bunri-u.ac.jp
COUNTRY OF AUTHOR: Japan; France
SOURCE: BIOLOGICAL CHEMISTRY, (JUN 2004) Vol. 385, No. 6, pp. 511-516.
ISSN: 1431-6730.
PUBLISHER: WALTER DE GRUYTER & CO, GENTHINER STRASSE 13, D-10785 BERLIN, GERMANY.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 23
ENTRY DATE: Entered STN: 6 Aug 2004
Last Updated on STN: 6 Aug 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The mammalian legumain is a recently identified lysosomal cysteine proteinase belonging to the clan CD and homologous to plant legumain. This enzyme has the characteristic of specifically hydrolyzing peptide bonds after asparagine residues. As in the case of papain-type cysteine proteinases, legumain is synthesized as an inactive zymogen, and processed into a mature form localized in lysosomes. However, the mechanism of its activation remains unclear. In this study, we analyze which types of proteinases may participate in the processing of legumain in rat primary cultured macrophages using various proteinase inhibitors after 24 h treatment with Bafilomycin A1, a vacuolar ATPase inhibitor. The processing of legumain in macrophages was accomplished by papain-type cysteine proteinases other than cathepsin B.

L4 ANSWER 33 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:817693 SCISEARCH
THE GENUINE ARTICLE: 852KH
TITLE: Discovery, structure and biological activities of the cyclotides
AUTHOR: Craik D J (Reprint)
CORPORATE SOURCE: Univ Queensland, Inst Mol Biosci, Brisbane, Qld 4072, Australia (Reprint)
AUTHOR: Daly N L; Mulvenna J; Plan M R; Trabi M
CORPORATE SOURCE: E-mail: d.craik@imb.uq.edu.au
COUNTRY OF AUTHOR: Australia
SOURCE: CURRENT PROTEIN & PEPTIDE SCIENCE, (OCT 2004) Vol. 5, No. 5, pp. 297-315.
ISSN: 1389-2037.
PUBLISHER: BENTHAM SCIENCE PUBL LTD, PO BOX 1673, 1200 BR HILVERSUM, NETHERLANDS.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 89
ENTRY DATE: Entered STN: 8 Oct 2004
Last Updated on STN: 8 Oct 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The cyclotides are a family of small disulfide rich proteins that

have a cyclic peptide backbone and a cystine knot formed by three conserved disulfide bonds. The combination of these two structural motifs contributes to the exceptional chemical, thermal and enzymatic stability of the cyclotides, which retain bioactivity after boiling. They were initially discovered based on native medicine or screening studies associated with some of their various activities, which include uterotonic action, anti-HIV activity, neurotensin antagonism, and cytotoxicity. They are present in plants from the Rubiaceae, Violaceae and Cucurbitaccae families and their natural function in plants appears to be in host defense: they have potent activity against certain insect pests and they also have antimicrobial activity. There are currently around 50 published sequences of cyclotides and their rate of discovery has been increasing over recent years. Ultimately the family may comprise thousands of members. This article describes the background to the discovery of the cyclotides, their structural characterization, chemical synthesis, genetic origin, biological activities and potential applications in the pharmaceutical and agricultural industries. Their unique topological features make them interesting from a protein folding perspective. Because of their highly stable peptide framework they might make useful templates in drug design programs, and their insecticidal activity opens the possibility of applications in crop protection.

L4 ANSWER 34 OF 63 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 2004292880 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15194187
TITLE: Two novel asparaginyl endopeptidase -like cysteine proteinases from the protist Trichomonas vaginalis: their evolutionary relationship within the clan CD cysteine proteinases.
AUTHOR: Leon-Felix Josefina; Ortega-Lopez Jaime; Orozco-Solis Ricardo; Arroyo Rossana
CORPORATE SOURCE: Departamento de Patologia Experimental, Centro de Investigacion y de Estudios Avanzados (CINVESTAV) del Instituto Politecnico Nacional (IPN), 2508, Col. San Pedro Zacatenco, Mexico, D.F. CP 07360, Mexico.
SOURCE: Gene, (2004 Jun 23) Vol. 335, pp. 25-35. Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (COMPARATIVE STUDY) Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AY326446; GENBANK-AY326447
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 15 Jun 2004 Last Updated on STN: 24 Aug 2004 Entered Medline: 23 Aug 2004

AB Cysteine proteinases (CPs) are important virulence factors of the protozoan parasite Trichomonas vaginalis. A total of six genes coding for cathepsin L-like CPs belonging to clan CA have been identified in T. vaginalis. At least 23 distinct spots with proteolytic activity have been detected by two-dimensional (2-D) substrate gel electrophoresis from in vitro grown parasites; however, only few of them have been characterized. In this work, we detected six spots with proteolytic activity and molecular weights between 25 and 35 kDa. The six proteinases correspond to two distinct CP families: the papain-like family, represented by four spots with pIs between 4.5 and 5.5; and the legumain-like family represented by two spots with pI 6.3 and 6.5. Next, we obtained two cDNAs encoding for legumain-like CPs from T. vaginalis, which were named Tvlegu-1 and Tvlegu-2. The size of these cDNA clones were 1225 and 1364 bp, which encoded for 388 and 415 amino acids, respectively. Their

putative translation products have molecular masses of 42.8 and 47.2 kDa, corresponding to inactive legumain-like CP precursors. The two sequences share approximately 40% identity at the amino acid level. These protein products can be classified within a branch of the legumain-like family in clan CD cysteine proteinases due to their sensitivity to specific proteinases inhibitors, their DNA sequences, and phylogenetic reconstruction. However, they do not correspond either to the typical asparaginyl endopeptidase or the glycosylphosphatidylinositol (GPI): protein transamidase subfamilies. These results suggest that the TVLEGU-1 and TVLEGU-2 peptidases are likely to be part of a new subfamily within the legumain-like family of clan CD cysteine proteinases. Furthermore, they could be one of the missing links between prokaryotic and eukaryotic CPs in clan CD enzymes.

L4 ANSWER 35 OF 63 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 2003433146 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12974392
TITLE: Novel cell-permeable acyloxymethylketone inhibitors of asparaginyl endopeptidase.
AUTHOR: Loak Kylie; Li Dongtao Ni; Manoury Benedicte; Billson Jeremy; Morton Fraser; Hewitt Ellen; Watts Colin
CORPORATE SOURCE: Medivir UK Ltd., Peterhouse Technology Park, 100 Fulbourn Road, Cambridge, CB1 9PT, UK.
SOURCE: Biological chemistry, (2003 Aug) Vol. 384, No. 8, pp. 1239-46.
Journal code: 9700112. ISSN: 1431-6730.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 17 Sep 2003
Last Updated on STN: 21 May 2004
Entered Medline: 20 May 2004
AB Mammalian asparaginyl endopeptidase (AEP) or legumain is a recently identified lysosomal cysteine protease belonging to clan CD. To date it has been shown to be involved in antigen presentation within class II MHC positive cells and in pro-protein processing. Further elucidation of the biological functions of the enzyme will require potent and selective inhibitors and thus we describe here new acyloxymethylketone inhibitors of AEP. The most potent of the series is 2,6-dimethyl-benzoic acid 3-benzyloxycarbonylamino-4-carbamoyl-2-oxo-butyl ester (MV026630) with a kobs/[I] value of 1.09 x 10(5) M(-1) s(-1). At low microM concentrations this compound is able to enter living cells and irreversibly inactivate AEP. We show that this results in inhibition of AEP autoactivation and in perturbation of the processing and presentation of T cell epitopes from both tetanus toxin and myelin basic protein.

L4 ANSWER 36 OF 63 MEDLINE on STN
ACCESSION NUMBER: 2003188106 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12705852
TITLE: Asparagine endopeptidase can initiate the removal of the MHC class II invariant chain chaperone.
AUTHOR: Manoury Benedicte; Mazzeo Daniela; Li Dongtao Ni; Billson Jeremy; Loak Kylie; Benaroch Philippe; Watts Colin
CORPORATE SOURCE: Division of Cell Biology and Immunology, School of Life Sciences, University of Dundee, Dow Street, United Kingdom.. b.manoury@dundee.ac.uk
SOURCE: Immunity, (2003 Apr) Vol. 18, No. 4, pp. 489-98.
Journal code: 9432918. ISSN: 1074-7613.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 23 Apr 2003
Last Updated on STN: 9 May 2003
Entered Medline: 8 May 2003

AB The invariant chain (Ii) chaperone for MHC class II molecules is crucial for their effective function. Equally important is its removal. Cathepsins S or L are known to be required for the final stages of Ii removal in different APCs, but the enzymes which initiate Ii processing have not been identified. Here we show that this step can be performed in B lymphocytes by asparagine endopeptidase (AEP), which targets different asparagine residues in the lumenal domain of human and mouse invariant chain. Inhibition of AEP activity slows invariant chain processing and hinders the expression of an antigenic peptide engineered to replace the groove binding region of Ii (CLIP). However, the initiation of Ii removal can also be performed by other proteases, reflecting the importance of this step.

L4 ANSWER 37 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:843747 SCISEARCH
THE GENUINE ARTICLE: 723JR
TITLE: Expression of sea anemone equistatin in potato. Effects of plant proteases on heterologous protein production
AUTHOR: Jongsma M A (Reprint)
CORPORATE SOURCE: Plant Res Int, POB 16, NL-6700 AA Wageningen, Netherlands (Reprint)
AUTHOR: Outchkourov N S; Rogelj B; Strukelj B
CORPORATE SOURCE: Plant Res Int, NL-6700 AA Wageningen, Netherlands; Jozef Stefan Inst, SI-1000 Ljubljana, Slovenia
COUNTRY OF AUTHOR: Netherlands; Slovenia
SOURCE: PLANT PHYSIOLOGY, (SEP 2003) Vol. 133, No. 1, pp. 379-390. ISSN: 0032-0889.
PUBLISHER: AMER SOC PLANT BIOLOGISTS, 15501 MONONA DRIVE, ROCKVILLE, MD 20855 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 53
ENTRY DATE: Entered STN: 10 Oct 2003
Last Updated on STN: 10 Oct 2003
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Plants are increasingly used as production platforms of various heterologous proteins, but rapid protein turnover can seriously limit the steady-state expression level. Little is known about specific plant proteases involved in this process. In an attempt to obtain potato (Solanum tuberosum cv Desiree) plants resistant to Colorado potato beetle (Leptinotarsa decemlineata Say) larvae, the protease inhibitor equistatin was expressed under the control of strong, light-inducible and constitutive promoters and was targeted to the secretory pathway with and without endoplasmic reticulum retention signal. All constructs yielded similar stepwise protein degradation patterns, which considerably reduced the amount of active inhibitor in planta and resulted in insufficient levels for resistance against Colorado potato beetle larvae. Affinity purification of the degradation products and N-terminal sequencing allowed the identification of the amino acid P-1-positions (asparagine [Asn]-13, lysine-56, Asn-82, and arginine-151) that were cleaved in planta. The proteases involved in the equistatin degradation were characterized with synthetic substrates and inhibitors. Kininogen domain 3 completely inhibited equistatin degradation

in vitro. The results indicate that arginine/lysine-specific and legumain-type Asn-specific cysteine proteases seriously impede the functional accumulation of recombinant equistatin in planta. General strategies to improve the resistance to proteases of heterologous proteins in plants are proposed.

L4 ANSWER 38 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:900907 SCISEARCH
THE GENUINE ARTICLE: 589BH
TITLE: Inhibition of mammalian legumain by Michael acceptors and AzaAsn-halomethylketones
AUTHOR: Demuth H U (Reprint)
CORPORATE SOURCE: Probiodrug AG, Weinbergweg 22 Bioctr, D-06120 Halle Saale, Germany (Reprint)
AUTHOR: Niestroj A J; Feussner K; Heiser U; Dando P M; Barrett A; Gerhartz B
CORPORATE SOURCE: Probiodrug AG, D-06120 Halle Saale, Germany; Babraham Inst, MRC, Mol Enzymol Lab, Cambridge CB2 4AT, England
COUNTRY OF AUTHOR: Germany; England
SOURCE: BIOLOGICAL CHEMISTRY, (JUL-AUG 2002) Vol. 383, No. 7-8, pp. 1205-1214.
ISSN: 1431-6730.
PUBLISHER: WALTER DE GRUYTER & CO, GENTHINER STRASSE 13, D-10785 BERLIN, GERMANY.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 38
ENTRY DATE: Entered STN: 26 Nov 2002
Last Updated on STN: 26 Nov 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Legumain is a lysosomal cysteine peptidase specific for an asparagine residue in the P-1-position. It has been classified as a member of clan CD peptidases due to predicted structural similarities to caspases and gingipains. So far, inhibition studies on legumain are limited by the use of endogenous inhibitors such as cystatin C. A series of Michael acceptor inhibitors based on the backbone CbzLAlaLAlaLAsn (Cbz= benzyloxycarbonyl) has been prepared and resulted in an irreversible inhibition of porcine legumain. Variation of the molecular size within the war head revealed the best inhibition for the compound containing the allyl ester (k(obs)/I=766 M(-1)s(-1)). To overcome cyclisation between the amide moiety of the Asn residue and the war head, several asparagine analogues have been synthesised. Integrated in halomethylketone inhibitors , azaasparagine is accepted by legumain in the P-1-position. The most potent inhibitor of this series, CbzLAlaLAlaAzaAsnchloromethylketone, displays a k(obs)/I value of 139 000 M(-1)s(-1). Other cysteine peptidases, such as papain and cathepsin B, are not inhibited by this compound at concentrations up to 100 muM. The synthetic inhibitors described here represent useful tools for the investigation of the structural and physiological properties of this unique asparaginespecific peptidase.

L4 ANSWER 39 OF 63 MEDLINE on STN
ACCESSION NUMBER: 2002085631 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11812994
TITLE: Destructive processing by asparagine endopeptidase limits presentation of a dominant T cell epitope in MBP.
AUTHOR: Manoury Benedicte; Mazzeo Daniela; Fugger Lars; Viner Nick; Ponsford Mary; Streeter Heather; Mazza Graziella; Wraith David C; Watts Colin
CORPORATE SOURCE: Division of Cell Biology and Immunology, Wellcome Trust

Biocentre, School of Life Sciences, University of Dundee, Dundee DD1 5EH, UK.
SOURCE: Nature immunology, (2002 Feb) Vol. 3, No. 2, pp. 169-74. Electronic Publication: 2002-01-14. Journal code: 100941354. ISSN: 1529-2908.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 29 Jan 2002
Last Updated on STN: 23 Feb 2002
Entered Medline: 22 Feb 2002

AB Little is known about the processing of putative human autoantigens and why tolerance is established to some T cell epitopes but not others. Here we show that a principal human HLA-DR2-restricted epitope--amino acids 85-99 of myelin basic protein, MBP(85-99)--contains a processing site for the cysteine protease asparagine endopeptidase (AEP). Presentation of this epitope by human antigen-presenting cells is inversely proportional to the amount of cellular AEP activity: inhibition of AEP in living cells greatly enhances presentation of the MBP(85-99) epitope, whereas overexpression of AEP diminishes presentation. These results indicate that central tolerance to this encephalitogenic MBP epitope may not be established because destructive processing limits its display in the thymus. Consistent with this hypothesis, AEP is expressed abundantly in thymic antigen-presenting cells.

L4 ANSWER 40 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:193069 SCISEARCH
THE GENUINE ARTICLE: 524LC
TITLE: Activation of Arabidopsis vacuolar processing enzyme by self-catalytic removal of an auto-inhibitory domain of the C-terminal propeptide
AUTHOR: Hara-Nishimura I (Reprint)
CORPORATE SOURCE: Kyoto Univ, Grad Sch Sci, Dept Bot, Kyoto 6068502, Japan (Reprint)
AUTHOR: Kuroyanagi M; Nishimura M
CORPORATE SOURCE: Natl Inst Basic Biol, Dept Cell Biol, Okazaki, Aichi 4448585, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: PLANT AND CELL PHYSIOLOGY, (FEB 2002) Vol. 43, No. 2, pp. 143-151. ISSN: 0032-0781.
PUBLISHER: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 64
ENTRY DATE: Entered STN: 13 Mar 2002
Last Updated on STN: 13 Mar 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Vacuolar processing enzyme (VPE) is a cysteine proteinase responsible for the maturation of various vacuolar proteins in higher plants. To clarify the mechanism of maturation and activation of VPE, we expressed the precursors of Arabidopsis gammaVPE in insect cells. The cells accumulated a glycosylated proprotein precursor (pVPE) and an unglycosylated preproprotein precursor (ppVPE) which might be unfolded. The N-terminal sequence of pVPE revealed that ppVPE had a 22-amino-acid signal peptide to be removed co-translationally. Under acidic conditions, the 56-kDa pVPE was self-catalytically converted to a 43-kDa intermediate

form (iVPE) and then to the 40-kDa mature form (mVPE). N-terminal sequencing of iVPE and mVPE showed that sequential removal of the C-terminal propeptide and N-terminal propeptide produced mVPE. Both iVPE and mVPE exhibited the activity, while pVPE exhibited no activity. These results imply that the removal of the C-terminal propeptide is essential for activating the enzyme. Further removal of the N-terminal propeptide from iVPE is not required to activate the enzyme. To demonstrate that the C-terminal propeptide functions as an inhibitor of VPE, we expressed the C-terminal propeptide and produced specific antibodies against it. We found that the C-terminal propeptide reduced the activity of VPE and that this inhibitory activity was suppressed by specific antibodies against it. Our findings suggest that the C-terminal propeptide functions as an auto-inhibitory domain that masks the catalytic site. Thus, the removal of the C-terminal propeptide of pVPE might expose the catalytic site of the enzyme.

L4 ANSWER 41 OF 63 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 2002244765 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11983426
TITLE: Legumain from bovine kidney: its purification, molecular cloning, immunohistochemical localization and degradation of annexin II and vitamin D-binding protein.
AUTHOR: Yamane Takuya; Takeuchi Keisuke; Yamamoto Yoshio; Li Yao-Hua; Fujiwara Manabu; Nishi Katuji; Takahashi Sho; Ohkubo Iwao
CORPORATE SOURCE: Department of Medical Biochemistry, Shiga University of Medical Science, Seta, Otsu 520-2192, Japan.
SOURCE: Biochimica et biophysica acta, (2002 Apr 1) Vol. 1596, No. 1, pp. 108-20.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB060129
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 2 May 2002
Last Updated on STN: 10 Jul 2002
Entered Medline: 9 Jul 2002

AB Legumain (asparaginyl endopeptidase) was purified to homogeneity from bovine kidneys. The molecular mass of the purified enzyme was calculated to be 34000 by sodium dodecyl sulfate-polyacrylamide gel electrophoresis in the presence of beta-mercaptoethanol. The enzyme rapidly hydrolyzed the substrate Z-Ala-Ala-Asn-MCA and was strongly inhibited by N-ethylmaleimide, p-chloromercuribenzene-sulfonic acid, Hg(2+) and Cu(2+). The amino acid sequence of the first 26 residues of the enzyme was Gly-Gly-Lys-His-Trp-Val-Val-Ile-Val-Ala-Gly-Ser-Asn-Gly-Gln-Tyr-Asn-Tyr-Arg-His-Gln-Ala-Phe-Ala-Asp-His-. This sequence is highly homologous to the sequences in the N-terminal of pig kidney legumain. We screened a bovine kidney cortex cDNA library using a DNA probe that originated from rat legumain, and we determined the bovine kidney cDNA structure and deduced the amino acid sequence. The cDNA is composed 1934 bp and encodes 433 amino acids in the coding region. The enzyme was strongly stained in the proximal tubules of the rat kidney in an immunohistochemical study. Vitamin D-binding protein which is known to be a ligand to megalin existing in the proximal tubules, was cleaved in a limited proteolytic manner by bovine kidney legumain. These results suggested that legumain contributes to the processing of macromolecules absorbed by proximal tubule cells. The enzyme also cleaved an N-terminal synthetic peptide of bovine annexin II

(Gly(24)-Ser-Val-Lys-Ala-Tyr-Thr(30)-Asn-Phe-Asp-Ala-Glu(35)-Arg-Asp(37)) at a position between Asn(31) and Phe(32). The amino-terminal domain of annexin II has p11 subunit binding sites and phosphorylation sites for both pp60(src) and protein kinase C. This suggests that legumain plays an important role in inactivation and degradation of annexin II, which is abundant in the receptor-recycling compartments of endosomes/lysosomes.

L4 ANSWER 42 OF 63 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 2001538268 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11585344
TITLE: Osteoclast inhibitory peptide 2 inhibits osteoclast formation via its C-terminal fragment.
AUTHOR: Choi S J; Kurihara N; Oba Y; Roodman G D
CORPORATE SOURCE: Department of Medicine/Hematology, University of Texas Health Science Center, San Antonio, USA.
SOURCE: Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, (2001 Oct) Vol. 16, No. 10, pp. 1804-11. Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 8 Oct 2001
Last Updated on STN: 27 Feb 2002
Entered Medline: 26 Feb 2002
AB Osteoclast inhibitory peptide 2 (OIP-2) is a novel autocrine/paracrine factor produced by osteoclasts (OCLs) that inhibits bone resorption and OCL formation in vitro and in vivo. It is identical to the asparaginyl endopeptidase legumain. During maturation of OIP-2, a signal peptide and a 17-kDa C-terminal fragment (CTF) are cleaved to produce the mature enzyme. To determine if enzyme activity is required for inhibition of OCL formation or if only the CTF is responsible for these effects, we synthesized His-tagged complementary DNA (cDNA) constructs for the CTF of OIP-2, the proform of OIP-2, and the "mature enzyme" form of OIP-2. The proform or the CTF portion of OIP-2 inhibited OCL formation in a dose-dependent manner in murine bone marrow cultures stimulated with 1,25-dihydroxyvitamin D3 [1,25(OH)2D3]. The mature form of OIP-2, which was enzymatically active, did not inhibit OCL formation. In addition, OIP-2 inhibited OCL formation in cultures of highly purified human OCL precursor cells or RAW264.7 cells stimulated with 10 ng/ml of receptor activator of NF-kappaB (RANK) ligand. Binding studies with His-tagged OIP-2 showed expression of a putative OIP-2 receptor on RAW264.7 cells treated with RANK ligand for 4 days and human marrow cultures treated with 1,25(OH)2D3 for 3 weeks. These data show that the CTF of OIP-2, rather than the mature enzyme, mediates the inhibitory effects of OIP-2 through a putative receptor on OCL precursors.

L4 ANSWER 43 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:747130 SCISEARCH
THE GENUINE ARTICLE: 471AW
TITLE: Stored proteinases and the initiation of storage protein mobilization in seeds during germination and seedling growth
AUTHOR: Muntz K (Reprint)
CORPORATE SOURCE: IPK, Corrensstr 3, D-06466 Gatersleben, Germany (Reprint)
AUTHOR: Belozersky M A; Dunaevsky Y E; Schlereth A; Tiedemann J
CORPORATE SOURCE: IPK, D-06466 Gatersleben, Germany; Moscow MV Lomonosov

State Univ, AN Belozersky Inst Physicochem Biol, Moscow 119899, Russia
COUNTRY OF AUTHOR: Germany; Russia
SOURCE: JOURNAL OF EXPERIMENTAL BOTANY, (SEP 2001) Vol. 52, No. 362, pp. 1741-1752.
ISSN: 0022-0957.
PUBLISHER: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 87
ENTRY DATE: Entered STN: 28 Sep 2001
Last Updated on STN: 28 Sep 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Though endopeptidases and carboxypeptidases are present in protein bodies of dry quiescent seeds the function of these proteases during germination is still a matter of debate. In some plants it was demonstrated that endopeptidases of dry protein bodies degrade storage proteins of these organelles. Other studies describe cases where this did not happen. The role that stored proteinases play in the initiation of storage protein breakdown in germinating seeds thus remains unclear. Numerous reviews state that the initiation of reserve protein mobilization is attributed to de novo formed endopeptidases which together with stored carboxypeptidases degrade the bulk of proteins in storage organs and tissues after seeds have germinated. The evidence that the small amounts of endopeptidases in protein bodies of embryonic axes and cotyledons of dry seeds from dicotyledonous plants play an important role in the initiation of storage protein mobilization during early germination is summarized here.

L4 ANSWER 44 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:618695 SCISEARCH
THE GENUINE ARTICLE: 457XN
TITLE: Legumain forms from plants and animals differ in their specificity
AUTHOR: Barrett A J (Reprint)
CORPORATE SOURCE: Babraham Inst, MRC, Mol Enzymol Lab, Cambridge CB2 4AT, England (Reprint)
AUTHOR: Rotari V I; Dando P M
CORPORATE SOURCE: State Univ Moldova, Prot Chem Lab, Kishinev 2009, Moldova
COUNTRY OF AUTHOR: England; Moldova
SOURCE: BIOLOGICAL CHEMISTRY, (JUN 2001) Vol. 382, No. 6, pp. 953-959.
ISSN: 1431-6730.
PUBLISHER: WALTER DE GRUYTER & CO, GENTHINER STRASSE 13, D-10785 BERLIN, GERMANY.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 33
ENTRY DATE: Entered STN: 17 Aug 2001
Last Updated on STN: 17 Aug 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We purified forms of legumain from a plant source (seeds of kidney bean, Phaseolus vulgaris) and a mammal (kidney of pig, Sus scropha) for comparison of their properties. Both forms were found to be stable only under moderately acidic pH conditions, and were maximally active at about pH 6; the plant enzyme was somewhat less stable and had a slightly higher pH optimum. With benzyloxycarbonyl-Xaa-Ala-Asn-aminomethylcoumarylamide substrates, the two forms of legumain showed distinctly different specificities for the P3 residue, the plant legumain preferring amino acids with bulky hydrophobic side chains because of lower K-m values.

Both forms of legumain were highly specific for hydrolysis of asparaginyl bonds in the arylamide substrates and in neurotensin. Aspartyl bonds were hydrolysed about 100-fold more slowly with lower pH optima. Potential substrates containing other amino acids structurally similar to asparagine were not hydrolysed. There were clear differences in specificity of hydrolysis of protein substrates. The plant legumain differed from pig legumain in its action on tetanus toxoid C-fragment, cleaving at Asn(97) but not at Asn(337), and produced more extensive digestion of phaseolin. The plant form of legumain was much more weakly inhibited by egg-white cystatin than was the mammalian form.

L4 ANSWER 45 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:575939 SCISEARCH
THE GENUINE ARTICLE: 453AR
TITLE: Activation of progelatinase A by mammalian legumain, a recently discovered cysteine proteinase
AUTHOR: Chen J M (Reprint)
CORPORATE SOURCE: Babraham Inst, MRC, Mol Enzymol Lab, Cambridge CB2 4AT, England (Reprint)
AUTHOR: Fortunato M; Stevens R A E; Barrett A J
COUNTRY OF AUTHOR: England
SOURCE: BIOLOGICAL CHEMISTRY, (MAY 2001) Vol. 382, No. 5, pp. 777-783.
ISSN: 1431-6730.
PUBLISHER: WALTER DE GRUYTER & CO, GENTHINER STRASSE 13, D-10785 BERLIN, GERMANY.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 34
ENTRY DATE: Entered STN: 3 Aug 2001
Last Updated on STN: 3 Aug 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The activation of progelatinase A to gelatinase A requires cleavage of an asparaginyl bond to form the N-terminus of the mature enzyme. We have asked whether the activation can be mediated by legumain, the recently discovered lysosomal cysteine proteinase that is specific for hydrolysis of asparaginyl bonds. Addition of purified legumain to the concentrated conditioned medium from HT1080 cell culture that contained both progelatinases A and B caused the conversion of the 72 kDa progelatinase A to the 62 kDa form. The progelatinase B in the medium was unaffected. Incubation of recombinant progelatinase A with legumain resulted in an almost instantaneous activation as judged by the fluorometric assay with a specific gelatinase A substrate, Mca-Pro-Leu-GlyLeu-Dpa-Ala-Arg-NH2. Legumain also activated progelatinase A when it was in complex with TIMP-2. Zymographic analysis and N-terminal sequencing revealed that legumain cleaved the 72 kDa progelatinase A at the bonds between Asn(109)-Tyr(110) or Asn(111)-Phe(112) to produce the 62 kDa mature enzyme, and that further cleavage at Asn(430) also occurred to generate a 36 kDa active form. More 62 kDa gelatinase A was detected in cultures of C13 cells that over-expressed legumain than in those of the control HEK293 cells. We conclude that legumain is clearly capable of processing progelatinase A to the active enzyme in vitro and in cultured cells.

L4 ANSWER 46 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:384120 SCISEARCH
THE GENUINE ARTICLE: 427HX
TITLE: Stored cysteine proteinases start globulin mobilization in protein bodies of embryonic axes and cotyledons during vetch (Vicia sativa L.) seed germination

AUTHOR: Muntz K (Reprint)
CORPORATE SOURCE: Inst Pflanzengenet & Kulturpflanzenforsch, Correnssstr 3, D-06466 Gatersleben, Germany (Reprint)
AUTHOR: Schlereth A; Standhardt D; Mock H P
CORPORATE SOURCE: Inst Pflanzengenet & Kulturpflanzenforsch, D-06466 Gatersleben, Germany
COUNTRY OF AUTHOR: Germany
SOURCE: PLANTA, (APR 2001) Vol. 212, No. 5-6, pp. 718-727. ISSN: 0032-0935.
PUBLISHER: SPRINGER-VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 47
ENTRY DATE: Entered STN: 18 May 2001
Last Updated on STN: 18 May 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Inhibition of protein synthesis by cycloheximide during vetch seed germination, did not prevent globulin breakdown as indicated by a decrease in vicilin-and legumin-specific immunosignals on Western blots. Protein bodies isolated from embryo axes and cotyledons of dry vetch (Vicia sativa L.) seeds using a non-aqueous method were found to be free of cytoplasmic and organellar contaminations. Lysates of these purified protein bodies were capable of degrading globulins; this process was blocked by the cysteine proteinase (CPR) inhibitor iodoacetic acid. Protein bodies contained the papain-like CPR2 and CPR4, and the legumain-like CPR VsPB2. In vitro assays showed that albumin extracts from protein bodies degraded oligopeptide substrates in the PepTag-Assay and degraded the legumain substrate N-benzoyl-asparaginyl-p-nitroanilide. We conclude that, during germination, globulin mobilization is initiated by stored CPRs in protein bodies of embryonic axes as well as cotyledons, and that de-novo-formed proteolytic globulin in cotyledons after germination.

L4 ANSWER 47 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:463594 SCISEARCH
THE GENUINE ARTICLE: 438WE
TITLE: Bm-CPI-2, a cystatin homolog secreted by the filarial parasite Brugia malayi, inhibits class II MHC-restricted antigen processing
AUTHOR: Watts C (Reprint)
CORPORATE SOURCE: Univ Dundee, Dept Biochem, Wellcome Trust Bioctr, Dundee DD1 5EH, Scotland (Reprint)
AUTHOR: Manoury B; Gregory W F; Maizels R M
CORPORATE SOURCE: Univ Edinburgh, Inst Cell Anim & Populat Biol, Edinburgh EH9 3JT, Midlothian, Scotland
COUNTRY OF AUTHOR: Scotland
SOURCE: CURRENT BIOLOGY, (20 MAR 2001) Vol. 11, No. 6, pp. 447-451 .
ISSN: 0960-9822.
PUBLISHER: CELL PRESS, 1100 MASSACHUSETTES AVE,, CAMBRIDGE, MA 02138 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 24
ENTRY DATE: Entered STN: 22 Jun 2001
Last Updated on STN: 22 Jun 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB While interference with the class I MHC pathway by pathogen-encoded gene products, especially those of viruses, has been well documented, few examples of specific interference with the MHC class II pathway have been reported, Potential targets for such interference are the proteases that

remove the invariant chain chaperone and generate antigenic peptides, Indeed, recent studies indicate that immature dendritic cells express cystatin C to modulate cysteine protease activity and the expression of class II MHC molecules [1], Here, we show that Bm-CPI-2, a recently discovered cystatin homolog produced by the filarial nematode parasite Brugia malayi (W, F. Gregory et al,, submitted), inhibits multiple cysteine protease activities found in the endosomes/lysosomes of human a lymphocyte lines. CPI-2 blocked the hydrolysis of synthetic substrates favored by two different families of lysosomal cysteine proteases and blocked the in vitro processing of the tetanus toxin antigen by purified lysosome fractions. Moreover, CPI-2 substantially inhibited the presentation of selected T cell epitopes from tetanus toxin by living antigen-presenting cells. Our studies provide the first example of a product from a eukaryotic parasite that can directly interfere with antigen presentation, which, in turn, may suggest how filarial parasites might inactivate the host immune response to a helminth invader.

L4 ANSWER 48 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:369394 SCISEARCH
THE GENUINE ARTICLE: 425BN
TITLE: Soybean subtilisin-like protease involved in initiating storage protein degradation
AUTHOR: Tan-Wilson A (Reprint)
CORPORATE SOURCE: SUNY Binghamton, Dept Biol Sci, Binghamton, NY 13902 USA (Reprint)
AUTHOR: Liu X W; Zhang Z; Barnaby N; Wilson K A
COUNTRY OF AUTHOR: USA
SOURCE: SEED SCIENCE RESEARCH, (MAR 2001) Vol. 11, No. 1, pp. 55-68.
ISSN: 0960-2585.
PUBLISHER: C A B I PUBLISHING, C/O PUBLISHING DIVISION, WALLINGFORD OX10 8DE, OXON, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 57
ENTRY DATE: Entered STN: 11 May 2001
Last Updated on STN: 11 May 2001

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A partial cDNA fragment (1.1 kb) of protease C1, an enzyme that initiates the proteolytic degradation of the beta -conglycinin storage proteins in the soybean (Glycine max [L.] Merrill. cv. Amsoy 71) through limited action at Glurich regions, has been cloned by reverse transcription-polymerase chain reaction (RT-PCR). The sequence was extended toward the 5' end by another 314 bases. The nucleotide sequence shows that protease C1 belongs to the subtilisin family of serine proteases. The sequence encompasses the critical Asp, His and Ser residues of the catalytic triad, as well as the Asn at the binding site. Northern analysis shows the presence of 2.5 kb mRNA not only in seedling also in developing seeds. The developing seeds, and even dry seeds. phenylmethylsulfonyl fluoride (PMSF) and EDTA-sensitive protease activity that only cleaves the alpha- and alpha'-, but not the beta -subunits, of soybean beta -conglycinin. The discrete proteolytic intermediates produced are of the same sizes as those produced by pure enzyme, as are the final 50 kDa and 48 kDa products. The activity is also sensitive to inhibition by synthetic poly-L-Glu, all characteristics of purified protease C1. These data suggest that protease C1, or an enzyme very similar to it. is synthesized in a form that is active in vitro. Because seeds do accumulate beta -conglycinin and because there is very little evidence of the proteolytic products of protease C1 action in extracts of dry seeds, one can surmise that the protease C1 is not

particularly active in vivo during seed maturation. GenBank lists the sequence of the 1.1 kb fragment with accession number AAD02075.

L4 ANSWER 49 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:99252 SCISEARCH
THE GENUINE ARTICLE: 395DW
TITLE: Antigen processing in the endocytic compartment
AUTHOR: Watts C (Reprint)
CORPORATE SOURCE: Univ Dundee, Wellcome Trust Bioctr, Dow St, Dundee DD1 5EH, Scotland (Reprint)
AUTHOR: Watts C (Reprint)
CORPORATE SOURCE: Univ Dundee, Wellcome Trust Bioctr, Dundee DD1 5EH, Scotland
COUNTRY OF AUTHOR: Scotland
SOURCE: CURRENT OPINION IN IMMUNOLOGY, (FEB 2001) Vol. 13, No. 1, pp. 26-31.
ISSN: 0952-7915.
PUBLISHER: CURRENT BIOLOGY LTD, 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 58
ENTRY DATE: Entered STN: 9 Feb 2001
Last Updated on STN: 9 Feb 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Proteolysis generates the peptides that bind to class II MHC molecules and, by destruction of the invariant chain, prepares the class II MHC molecule for capture of those peptides. A clearer picture is emerging of the proteases, protease inhibitors and other factors that together control the environment for class II MHC peptide loading. However, the details of invariant-chain processing and antigen processing may differ depending on the allele of class II and the antigen substrate under consideration.

L4 ANSWER 50 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:12318 SCISEARCH
THE GENUINE ARTICLE: 385VC
TITLE: Activation of human prolegumain by cleavage at a C-terminal asparagine residue
AUTHOR: Chen J M (Reprint)
CORPORATE SOURCE: Babraham Inst, MRC, Mol Enzymol Lab, Cambridge CB2 4AT, England (Reprint)
AUTHOR: Fortunato M; Barrett A J
COUNTRY OF AUTHOR: England
SOURCE: BIOCHEMICAL JOURNAL, (1 DEC 2000) Vol. 352, Part 2, pp. 327-334.
ISSN: 0264-6021.
PUBLISHER: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON W1N 3AJ, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 36
ENTRY DATE: Entered STN: 12 Jan 2001
Last Updated on STN: 12 Jan 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The processing and activation of prolegumain were studied using the recombinant protein synthesized by cells that had been stably transfected with a human legumain cDNA construct. A cell line termed C13 was selected for the high-level expression of prolegumain. C13 cells produced primarily 56 kDa prolegumain. The 56 kDa form was enzymically inactive

but stable at neutral pH, unlike the 35 kDa mature pig legumain; it could be converted into a 46 kDa active form by incubation at pH 4.5. The 56 kDa pro-form and the 46 kDa active form were found to have the same N-terminal amino acid sequence, indicating that cleavage at the N-terminus was not necessary for prolegumain activation, and that the decrease in molecular mass was due to a C-terminal cleavage. The C-terminal processing site was identified as Asn(323). Replacement of Asn(323) at the cleavage site with aspartate, serine, alanine or glutamate abolished the processing and activation of prolegumain. In contrast, mutation of other asparagine and aspartate residues near the cleavage site had no effect. These results demonstrate that Asn(323) is essential for prolegumain activation.

L4 ANSWER 51 OF 63 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 1999419060 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10488118
TITLE: Identification of human asparaginyl endopeptidase (legumain) as an inhibitor of osteoclast formation and bone resorption.
AUTHOR: Choi S J; Reddy S V; Devlin R D; Menaa C; Chung H; Boyce B F; Roodman G D
CORPORATE SOURCE: Department of Medicine/Hematology, University of Texas Health Science Center, San Antonio, Texas 78284, USA.
CONTRACT NUMBER: AG13625 (United States NIA)
AR41336 (United States NIAMS)
AR44603 (United States NIAMS)
SOURCE: The Journal of biological chemistry, (1999 Sep 24) Vol. 274, No. 39, pp. 27747-53.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 11 Jan 2000
Last Updated on STN: 11 Jan 2000
Entered Medline: 4 Nov 1999

AB We screened a human osteoclast (OCL) cDNA expression library for OCL inhibitory factors and identified a clone that blocked both human and murine OCL formation and bone resorption by more than 60%. This clone was identical to human legumain, a cysteine endopeptidase. Legumain significantly inhibited OCL-like multinucleated cell formation induced by 1,25-dihydroxyvitamin D(3) (1,25-(OH)(2)D(3)) and parathyroid hormone-related protein (PTHrP) in mouse and human bone marrow cultures, and bone resorption in the fetal rat long bone assay in a dose-dependent manner. Legumain was detected in freshly isolated marrow plasma from normal donors and conditioned media from human marrow cultures. Furthermore, treatment of human marrow cultures with an antibody to legumain induced OCL formation to levels that were as high as those induced by 1,25-(OH)(2)D(3). Implantation in nude mice of 293 cells transfected with the legumain cDNA and constitutively expressing high levels of the protein significantly reduced hypercalcemia induced by PTHrP by about 50%, and significantly inhibited the increase in OCL surface and in OCL number expressed per mm(2) bone area and per mm bone surface induced by PTHrP. These results suggest that legumain may be a physiologic local regulator of OCL activity that can negatively modulate OCL formation and activity.

L4 ANSWER 52 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:500697 SCISEARCH
THE GENUINE ARTICLE: 212BK
TITLE: Inhibition of mammalian legumain by some cystatins is due to a novel second reactive site
AUTHOR: Abrahamson M (Reprint)
CORPORATE SOURCE: Univ Lund Hosp, Inst Lab Med, Dept Clin Chem, S-22185 Lund, Sweden (Reprint)
AUTHOR: Alvarez-Fernandez M; Barrett A J; Gerhartz B; Dando P M; Ni J A
CORPORATE SOURCE: Babraham Inst, MRC, Mol Enzymol Lab, Cambridge CB2 4AT, England; Human Genome Sci Inc, Rockville, MD 20850 USA
COUNTRY OF AUTHOR: Sweden; England; USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2 JUL 1999) Vol. 274, No. 27, pp. 19195-19203.
ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 55
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have investigated the inhibition of the recently identified family C13 cysteine peptidase, pig legumain, by human cystatin C, The cystatin was seen to inhibit enzyme activity by stoichiometric 1:1 binding in competition with substrate. The K-i value for the interaction was 0.20 nM, i.e. cystatin C had an affinity for legumain similar to that for the papain-like family C1 cysteine peptidase, cathepsin B, However, cystatin C variants with alterations in the N-terminal region and the "second hairpin loop" that rendered the cystatin inactive against cathepsin B, still inhibited legumain with K-i values 0.2-0.3 nM. Complexes between cystatin C and papain inhibited legumain activity against benzoyl-Asn-NHPhNO2, as efficiently as did cystatin C alone, Conversely, cystatin C inhibited papain activity against benzoyl-Arg-NHPhNO2 whether or not the cystatin had been incubated with legumain, strongly indicating that the cystatin inhibited the two enzymes with non-overlapping sites. A ternary complex between legumain, cystatin C, and papain was demonstrated by gel filtration supported by immunoblotting. Screening of a panel of cystatin superfamily members showed that type 1 inhibitors (cystatins A and B) and low M-r kininogen (type 3) did not inhibit pig legumain, Of human type 2 cystatins, cystatin D was non-inhibitory, whereas cystatin E/M and cystatin F displayed strong (K-i 0.0016 nM) and relatively weak (K-i 10 nM) affinity for legumain, respectively. Sequence alignments and molecular modeling led to the suggestion that a loop located on the opposite side to the papain-binding surface, between the alpha-helix and the first strand of the main beta-pleated sheet of the cystatin structure, could be involved in legumain binding. This was corroborated by analysis of a cystatin C variant with substitution of the Asn(39) residue in this loop (N39K-cystatin C); this variant showed a slight reduction in affinity for cathepsin B (K-i 1.5 nM) but much greater than 5,000-fold lower affinity for legumain (K-i much greater than 1,000 nM) than wild-type cystatin C.

L4 ANSWER 53 OF 63 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 1999434135 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10502678
TITLE: Identification and possible roles of three types of endopeptidase from germinated wheat seeds.
AUTHOR: Sutoh K; Kato H; Minamikawa T
CORPORATE SOURCE: Department of Biological Sciences, Tokyo Metropolitan

University, Minami-ohsawa, Hachioji, Tokyo, 192-0397, Japan.
SOURCE: Journal of biochemistry, (1999 Oct) Vol. 126, No. 4, pp. 700-7.
Journal code: 0376600. ISSN: 0021-924X.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 14 Jan 2000
Last Updated on STN: 14 Jan 2000
Entered Medline: 30 Dec 1999

AB Little or no endopeptidase activity was detected in extracts of dry mature wheat seeds, but when they were allowed to imbibe water in darkness, the activity expressed per seedling increased notably after d 1, reached a maximum on d 3 and then decreased. Two major endopeptidases, named WEP-1 and WEP-2, were present in the 50-70% saturated ammonium sulfate fraction of d-3 seedlings, and could be separated by hydrophobic column chromatography. WEP-1 was further purified and identified as a 31-kDa polypeptide that was immunoreactive to antiserum raised against REP-1, a major rice cysteine endopeptidase. Experiments with proteinase inhibitors revealed that WEP-1 and WEP-2 are cysteine and serine endopeptidases, respectively. The two enzymes differed in substrate specificity, pH dependence, and the ability to digest major wheat seed proteins. Determination of its amino-terminal amino acid sequence indicated the similarity of WEP-1 to other cereal cysteine endopeptidases which are involved in the digestion of seed storage proteins. The expression of WEP-1 in de-embryonated seeds was induced in the presence of gibberellic acid and its effect was eliminated by abscisic acid. In addition to WEP-1 and WEP-2, a legumain-like asparaginyl endopeptidase was identified in the extract of seedlings on hydrophobic chromatography. The asparaginyl endopeptidase may function in the early step of mobilization of wheat storage proteins in germinated seeds.

L4 ANSWER 54 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:713452 SCISEARCH
THE GENUINE ARTICLE: 238MA
TITLE: Colorimetric and fluorimetric microplate assays for legumain and a staining reaction for detection of the enzyme after electrophoresis
AUTHOR: Barrett A J (Reprint)
CORPORATE SOURCE: Babraham Inst, Mol Enzymol Lab, MRC, Babraham CB2 4AT, Cambs, England (Reprint)
AUTHOR: Johansen H T; Knight C G
CORPORATE SOURCE: Univ Cambridge, Dept Biochem, Cambridge CB2 1QW, England; Univ Oslo, Sch Pharm, N-0316 Oslo, Norway
COUNTRY OF AUTHOR: England; Norway
SOURCE: ANALYTICAL BIOCHEMISTRY, (10 SEP 1999) Vol. 273, No. 2, pp. 278-283.
ISSN: 0003-2697.
PUBLISHER: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 19
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The cysteine endopeptidase legumain was recently discovered in mammalian cells, predominantly localized in the lysosomal system where it is believed to contribute to antigen processing for MHC class II. Here we describe rapid assay procedures for the enzyme in 96-well microplates with two substrates, a novel compound, succinyl-Ala-Ala-Asn-4-methoxy-2-naphthylamide, and benzyloxycarbonyl-Ala-Ala-Asn-4-methyl-7-coumarylamide. Both substrates are suitable for fluorimetric assays, but the naphthylamide also allows colorimetric detection of legumain activity, since the released 4-methoxy-2-naphthylamine gives a red product when coupled with the Fast Garnet color reagent. We show that the naphthylamide substrate can be used to visualize active legumain after electrophoresis in polyacrylamide gel. Both substrates provide assays that are reproducible and sufficiently sensitive to allow the assay of legumain in crude samples such as tissue homogenates, although the coumarylamide is the more sensitive. The specificity of both assay methods for legumain was verified by the lack of inhibition by E-64 and total inhibition by eggwhite cystatin. (C) 1999 Academic Press.

L4 ANSWER 55 OF 63 MEDLINE on STN DUPLICATE 23
ACCESSION NUMBER: 1999178794 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10080709
TITLE: Molecular cloning and characterization of Vigna mungo processing enzyme 1 (VmPE-1), an asparaginyl endopeptidase possibly involved in post-translational processing of a vacuolar cysteine endopeptidase (SH-EP).
AUTHOR: Okamoto T; Minamikawa T
CORPORATE SOURCE: Department of Biology, Tokyo Metropolitan University, Hachioji, Japan.
SOURCE: Plant molecular biology, (1999 Jan) Vol. 39, No. 1, pp. 63-73.
Journal code: 9106343. ISSN: 0167-4412.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-D89971; GENBANK-D89972
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 13 Apr 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 1 Apr 1999

AB Asparaginyl endopeptidase is a cysteine endopeptidase that has strict substrate specificity toward the carboxy side of asparagine residues. Vigna mungo processing enzyme 1, termed VmPE-1, occurs in the cotyledons of germinated seeds of V. mungo, and is possibly involved in the post-translational processing of a vacuolar cysteine endopeptidase, designated SH-EP, which degrades seed storage protein. VmPE-1 also showed a substrate specificity to asparagine residues, and its enzymatic activity was inhibited by NEM but not E-64. In addition, purified VmPE-1 had a potential to process the recombinant SH-EP precursor to its intermediate in vitro. cDNA clones for VmPE-1 and its homologue, named VmPE-1A, were identified and sequenced, and their expressions in the cotyledons of V. mungo seedlings and other organs were investigated. VmPE-1 mRNA and SH-EP mRNA were expressed in germinated seeds at the same stage of germination although the enzymatic activity of VmPE-1 rose prior to that of SH-EP. The level of VmPE-1A mRNA continued increasing as germination proceeded. In roots, stems and leaves of fully grown plants, and in hypocotyls, VmPE-1 and VmPE-1A were little expressed. We discuss possible functions of VmPE-1 and VmPE-1A in the cotyledons of germinated seeds.

L4 ANSWER 56 OF 63 MEDLINE on STN DUPLICATE 24
ACCESSION NUMBER: 1999087325 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9872320
TITLE: An asparaginyl endopeptidase processes a microbial antigen for class II MHC presentation.
AUTHOR: Manoury B; Hewitt E W; Morrice N; Dando P M; Barrett A J; Watts C
CORPORATE SOURCE: Department of Biochemistry, University of Dundee, UK.
SOURCE: Nature, (1998 Dec 17) Vol. 396, No. 6712, pp. 695-9. Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 2 Feb 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 19 Jan 1999

AB Foreign protein antigens must be broken down within endosomes or lysosomes to generate suitable peptides that will form complexes with class II major histocompatibility complex molecules for presentation to T cells. However, it is not known which proteases are required for antigen processing. To investigate this, we exposed a domain of the microbial tetanus toxin antigen (TTCF) to disrupted lysosomes that had been purified from a human B-cell line. Here we show that the dominant processing activity is not one of the known lysosomal cathepsins, which are generally believed to be the principal enzymes involved in antigen processing, but is instead an asparagine-specific cysteine endopeptidase. This enzyme seems similar or identical to a mammalian homologue of the legumain/haemoglobinase asparaginyl endopeptidases found originally in plants and parasites. We designed competitive peptide inhibitors of B-cell asparaginyl endopeptidase (AEP) that specifically block its proteolytic activity and inhibit processing of TTCF in vitro. In vivo, these inhibitors slow TTCF presentation to T cells, whereas preprocessing of TTCF with AEP accelerates its presentation, indicating that this enzyme performs a key step in TTCF processing. We also show that N-glycosylation of asparagine residues blocks AEP action in vitro. This indicates that N-glycosylation could eliminate sites of processing by AEP in mammalian proteins, allowing preferential processing of microbial antigens.

L4 ANSWER 57 OF 63 MEDLINE on STN DUPLICATE 25
ACCESSION NUMBER: 1997218252 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9065484
TITLE: Cloning, isolation, and characterization of mammalian legumain, an asparaginyl endopeptidase.
AUTHOR: Chen J M; Dando P M; Rawlings N D; Brown M A; Young N E; Stevens R A; Hewitt E; Watts C; Barrett A J
CORPORATE SOURCE: Medical Research Council Peptidase Laboratory, Department of Immunology, The Babraham Institute, Babraham Hall, Babraham, Cambridgeshire CB2 4AT, United Kingdom.
SOURCE: The Journal of biological chemistry, (1997 Mar 21) Vol. 272, No. 12, pp. 8090-8. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-Y09862
ENTRY MONTH: 199704

ENTRY DATE: Entered STN: 6 May 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 18 Apr 1997

AB Legumain is a cysteine endopeptidase that shows strict specificity for hydrolysis of asparaginyl bonds. The enzyme belongs to peptidase family C13, and is thus unrelated to the better known cysteine peptidases of the papain family, C1 (Rawlings, N. D., and Barrett, A. J. (1994) Methods Enzymol. 244, 461-486). To date, legumain has been described only from plants and a blood fluke, Schistosoma mansoni. We now show that legumain is present in mammals. We have cloned and sequenced human legumain and part of pig legumain. We have also purified legumain to homogeneity (2200-fold, 8% yield) from pig kidney. The mammalian sequences are clearly homologous with legumains from non-mammalian species. Pig legumain is a glycoprotein of about 34 kDa, decreasing to 31 kDa on deglycosylation. It is an asparaginyl endopeptidase, hydrolyzing Z-Ala-Ala-Asn-7-(4-methyl)coumarylamide and benzoyl-Asn-p-nitroanilide. Maximal activity is seen at pH 5.8 under normal assay conditions, and the enzyme is irreversibly denatured at pH 7 and above. Mammalian legumain is a cysteine endopeptidase, inhibited by iodoacetamide and maleimides, but unaffected by compound E64 (trans-epoxysuccinyl-L-leucylamido-(4-guanidino)butane). It is inhibited by ovocystatin (cystatin from chicken egg white) and human cystatin C with Ki values < 5 nM. We discuss the significance of the discovery of a cysteine endopeptidase of a new family and distinctive specificity in man and other mammals.

L4 ANSWER 58 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:789099 SCISEARCH
THE GENUINE ARTICLE: YC390
TITLE: Characterization of endoproteases from plant peroxisomes
AUTHOR: Distefano S (Reprint); Palma J M; Gomez M; delRio L A
CORPORATE SOURCE: CSIC, ESTAC EXPT ZAIDIN, DEPT BIOQUIM BIOL CELULAR & MOL PLANTAS, E-18080 GRANADA, SPAIN; CSIC, ESTAC EXPT ZAIDIN, DEPT AGROECOL & PROTECC VEGETAL, E-18080 GRANADA, SPAIN
COUNTRY OF AUTHOR: SPAIN
SOURCE: BIOCHEMICAL JOURNAL, (15 OCT 1997) Vol. 327, Part 2, pp. 399-405.
ISSN: 0264-6021.
PUBLISHER: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON, ENGLAND W1N 3AJ .
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 57
ENTRY DATE: Entered STN: 1997
Last Updated on STN: 1997
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In this work, the characterization of endoprotease (EP) isoenzymes in peroxisomes is reported for the first time in cell organelles purified from pea leaves (Pisum sativum L.). A comparative analysis of the endo-proteolytic activity in peroxisomes purified from young (15-day-old) and senescent (50-day-old) leaves was carried out. Peroxisomes purified from senescent leaves showed a much higher endo-proteolytic activity than organelles from young plants. A 16 h incubation with exogenous substrates was the threshold time for the detection of a linear increase in the endo-proteolytic activity of peroxisomes from senescent leaves. Three EP isoenzymes (EP2, EP4 and EP5), having molecular masses of 88, 64 and 50 kDa respectively, were found in young plants by using SD S/polyacrylamide-gradient gels co-polymerized with gelatin. However, four additional isoenzymes (EP1, EP3, EP6 and EP7), with molecular masses of 220, 76, 46 and 34 kDa respectively, were detected in senescent plants.

All the isoenzymes detected in peroxisomes from both young and senescent leaves were neutral proteases. By using different class-specific inhibitors, the electrophoretically separated EP isoenzymes were characterized as three serine-proteinases (EP1, EP3 and EP4), two cysteine-proteinases (EP2 and EP6) and a metallo-proteinase (EP7), and EP5 might be a metal-dependent serine-proteinase. Moreover, a peroxisomal polypeptide of 64 kDa was recognized by an antibody against a thiol-protease. The serine-proteinase isoenzymes (EP1, EP3 and EP4), which represent approx. 70% of the total EP activity of peroxisomes, showed a notable thermal stability, not being inhibited by incubation at 50 degrees C for 1 h.

L4 ANSWER 59 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 1995:265173 SCISEARCH
THE GENUINE ARTICLE: QT470
TITLE: VACUOLAR PROCESSING ENZYME RESPONSIBLE FOR MATURATION OF SEED PROTEINS
AUTHOR: HARANISHIMURA I (Reprint)
CORPORATE SOURCE: NATL INST BASIC BIOL, DEPT CELL BIOL, OKAZAKI, AICHI 444, JAPAN (Reprint)
AUTHOR: SHIMADA T; HIRAIWA N; NISHIMURA M
CORPORATE SOURCE: GRAD UNIV ADV STUDIES, SCH LIFE SCI, DEPT MOLEC BIOMECH, OKAZAKI, AICHI 444, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: JOURNAL OF PLANT PHYSIOLOGY, (MAR 1995) Vol. 145, No. 5-6, pp. 632-640.
ISSN: 0176-1617.
PUBLISHER: GUSTAV FISCHER VERLAG, WOLLGRASWEG 49 POSTFACH 72 01 43, D-70577 STUTTGART, GERMANY.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; AGRI
LANGUAGE: English
REFERENCE COUNT: 55
ENTRY DATE: Entered STN: 1995
Last Updated on STN: 1995
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A vacuolar processing enzyme responsible for maturation of seed proteins was isolated from the castor bean and soybean. The processing enzyme belongs to a novel cysteine proteinase with a molecular mass of 37 kDa for castor bean and 39 kDa for soybean. The enzyme splits a peptide bond on the C-terminal side of an exposed asparagine residue of the proprotein precursors to produce their mature seed proteins such as 11S globulin and 25 albumin. Immunocytochemical localization bf the enzyme in the vacuolar matrix of maturing castor bean endosperm indicates that the maturation of the seed proteins occurs in the vacuoles. Molecular characterization revealed that the enzyme is synthesized as an inactive precursor with a larger molecular mass. The results of immunoelectron microscopic analysis suggested that the precursor is transported to vacuoles via dense vesicles together with proproteins of seed proteins. After arriving at the vacuoles, the inactive precursor is converted into an active enzyme. This suggests that a cascade for proprotein processing is involved in the maturation of seed proteins. Vacuolar processing enzyme activity was found in various plant tissues and several cDNA homologues of the enzyme were isolated from different plants. Thus a similar processing enzyme is widely distributed in plant tissues and plays a crucial role in the maturation of a variety of proteins in plant vacuoles.

L4 ANSWER 60 OF 63 MEDLINE on STN DUPLICATE 26

ACCESSION NUMBER: 1996132136 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8559590

TITLE: Asparaginyl endopeptidase activity in adult Schistosoma mansoni.
AUTHOR: Dalton J P; Hola-Jamriska L; Brindley P J
CORPORATE SOURCE: Molecular Parasitology Unit, Queensland Institute of Medical Research, Bancroft Centre, Royal Brisbane Hospital, Australia.
SOURCE: Parasitology, (1995 Dec) Vol. 111 (Pt 5), pp. 575-80. Journal code: 0401121. ISSN: 0031-1820.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 12 Mar 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 27 Feb 1996

AB Sequence comparisons have recently shown that the Schistosoma mansoni protein Sm32 is similar to asparaginyl endoproteinases, a novel family of cysteine proteinases, of which the legumains from legumes are the best characterized. By synthesizing and employing fluorogenic peptide substrates for the specific detection of asparaginyl endopeptidases, we have identified this type of activity in extracts of adult S. mansoni. The S. mansoni activity is similar to that of the legumains in its substrate specificity and sensitivity to thiol inhibitors, but differs in its pH and temperature optima for activity. In contrast, unlike the legumains, the schistosome asparaginyl endopeptidase activity is not activated by the reducing agent dithiothreitol. As suggested for legumains, Sm32 may function in the post-translational modification processes that regulate the activity of other molecules.

L4 ANSWER 61 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 27
ACCESSION NUMBER: 1995:76212 SCISEARCH
THE GENUINE ARTICLE: BB94F
TITLE: LEGUMAIN - ASPARAGINYL ENDOPEPTIDASE
AUTHOR: ISHII S (Reprint)
CORPORATE SOURCE: HOKKAIDO UNIV, FAC PHARMACEUT SCI, KITA 12, SAPPORO, HOKKAIDO 060, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: PROTEOLYTIC ENZYMES: SERINE AND CYSTEINE PEPTIDASES, (1994) Vol. 244, pp. 604-615. ISSN: 0076-6879.
PUBLISHER: ACADEMIC PRESS INC, 525 B STREET, SUITE 1900, SAN DIEGO, CA 92101-4495.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 23
ENTRY DATE: Entered STN: 1995
Last Updated on STN: 1995

L4 ANSWER 62 OF 63 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1994:503862 SCISEARCH
THE GENUINE ARTICLE: PB337
TITLE: CHARACTERIZATION OF ASPARAGINYL ENDOPEPTIDASE ACTIVITY IN ENDOSPERM OF DEVELOPING AND GERMINATING CASTOR-OIL SEEDS
AUTHOR: CORNEL F A (Reprint); PLAXTON W C
CORPORATE SOURCE: QUEENS UNIV, DEPT BIOL, KINGSTON K7L 3N6, ON, CANADA; QUEENS UNIV, DEPT BIOCHEM, KINGSTON K7L 3N6, ON, CANADA

COUNTRY OF AUTHOR: CANADA
SOURCE: PHYSIOLOGIA PLANTARUM, (AUG 1994) Vol. 91, No. 4, pp. 599-604.
ISSN: 0031-9317.
PUBLISHER: BLACKWELL MUNKSGAARD, 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 23
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A spectrophotometric assay was devised to characterize the asparaginyl (Asn) endopeptidase activity from the endosperm of castor oil seeds (Ricinus communis L. var. Baker 296). The assay measures the release of p-nitroaniline from the hydrolysis of benzoyl-L-Asn-p-nitroanilide. Assay sensitivity was improved through diazotization of the reaction product with N(1-napthyl)-ethylenediamine dihydrochloride; diazotized p-nitroaniline was determined spectrophotometrically at 548 nm (epsilon(548) = 1.64 x 10(4) M(-1)cm(-1)). By using this assay, Asn endopeptidase activity was detected in endosperm extracts of developing, mature and germinating castor seeds. Comparison of the Asn endopeptidase activities of developing and germinating castor endosperms revealed that they: 1) have identical pH-activity profiles with optimal activity occurring at pH 5.4; 2) are hear-labile proteins displaying comparable thermal stability profiles; and 3) are activated and inhibited by dithiothreitol and thiol modifying reagents, respectively. Thus, the Asn endopeptidases of developing and germinating castor seeds ru e very similar, if not identical, cysteine proteases. The most significant increase in the activity of endosperm Asn endopeptidase occurs during the full cotyledon to maturation stage of seed development; this period coincides with the most active phase of reserve protein accumulation by ripening castor oil seeds. Asn endopeptidase activity of fully mature (dry) castor seeds was about 2-fold lower than that of maturation stage ripening castor oil seed. Asn endopeptidase activity showed a slight reduction over the initial 2-day period following seed imbibition, and then rapidly decreased over the next several days of germination. The results are compatible with the proposal that Asn endopeptidase functions both to process storage preproteins following their import into protein bodies of developing seeds, as well as to participate in the mobilization of storage proteins during the early phase of seed germination.

L4 ANSWER 63 OF 63 MEDLINE on STN DUPLICATE 28
ACCESSION NUMBER: 1993155205 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8429028
TITLE: Asparaginyl endopeptidase of jack bean seeds. Purification, characterization, and high utility in protein sequence analysis.
AUTHOR: Abe Y; Shirane K; Yokosawa H; Matsushita H; Mitta M; Kato I; Ishii S
CORPORATE SOURCE: Department of Biochemistry, Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan.
SOURCE: The Journal of biological chemistry, (1993 Feb 15) Vol. 268, No. 5, pp. 3525-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L05515

ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 26 Mar 1993
Last Updated on STN: 3 Mar 2000
Entered Medline: 9 Mar 1993

AB Asparaginyl endopeptidase was highly purified from mature seeds of the jack bean (Canavalia ensiformis). The final enzyme preparation showed a single peak in high-performance liquid chromatography on a reversed-phase column, and the material in the peak gave the following NH2-terminal amino acid sequence on Edman degradation for 25 cycles: H-Glu-Val-Gly-Thr-Arg-Trp-Ala-Val-Leu-Val-Ala-Gly-Ser-Asn-Gly-Tyr-Gly-Asn-Tyr- Arg-His-Gln-Ala-Asp-Val-. Behavior of the enzyme toward various protease inhibitors suggested that it belongs to a family of cysteine proteases. Strict substrate specificity of this enzyme was verified by the use of 14 polypeptide substrates including those derived from proteins. Almost all the peptide bonds on the carboxyl side of Asn residues were susceptible to the enzyme. The exceptions were cases where the residue was at the NH2 terminus or the second position from the NH2 terminus of substrates and where it was N-glycosylated Asn. Peptide bonds on the carboxyl side of any other amino acid residues were not cleaved. These properties promise the high utility of this novel endopeptidase in protein sequence analysis. Identity of jack bean asparaginyl endopeptidase with a processing enzyme responsible for maturation of concanavalin A from its precursor is also discussed.

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 NEWS  3  OCT 07  EPFULL enhanced with full implementation of EPC2000
 NEWS  4  OCT 07  Multiple databases enhanced for more flexible patent
                  number searching
 NEWS  5  OCT 22  Current-awareness alert (SDI) setup and editing
                  enhanced
 NEWS  6  OCT 22  WPIDS, WPINDEX, and WPIX enhanced with Canadian PCT
                  Applications
 NEWS  7  OCT 24  CHEMLIST enhanced with intermediate list of
                  pre-registered REACH substances
 NEWS  8  NOV 21  CAS patent coverage to include exemplified prophetic
                  substances identified in English-, French-, German-,
                  and Japanese-language basic patents from 2004-present
 NEWS  9  NOV 26  MARPAT enhanced with FSORT command
 NEWS 10  NOV 26  MEDLINE year-end processing temporarily halts
                  availability of new fully-indexed citations
 NEWS 11  NOV 26  CHEMSAFE now available on STN Easy
 NEWS 12  NOV 26  Two new SET commands increase convenience of STN
                  searching
 NEWS 13  DEC 01  ChemPort single article sales feature unavailable
 NEWS 14  DEC 12  GBFULL now offers single source for full-text
                  coverage of complete UK patent families
 NEWS 15  DEC 17  Fifty-one pharmaceutical ingredients added to PS

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=> s asparaginyl endopeptidase
L1          271 ASPARAGINYL ENDOPEPTIDASE

=> s cystatin c
L2         5814 CYSTATIN C
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=> s l1 and l2
L3          13 L1 AND L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4           9 DUP REM L3 (4 DUPLICATES REMOVED)

=> d ibib abs 1-9

L4   ANSWER 1 OF 9     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:    2006331066     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 16565075
TITLE:               Cystatin M/E is a high affinity inhibitor of cathepsin V
                     and cathepsin L by a reactive site that is distinct from
                     the legumain-binding site. A novel clue for the role of
                     cystatin M/E in epidermal cornification.
AUTHOR:              Cheng Tsing; Hitomi Kiyotaka; van Vlijmen-Willems Ivonne M
                     J J; de Jongh Gys J; Yamamoto Kanae; Nishi Koji; Watts
                     Colin; Reinheckel Thomas; Schalkwijk Joost; Zeeuwen Patrick
                     L J M
CORPORATE SOURCE:    Department of Dermatology, Nijmegen Centre for Molecular
                     Life Sciences, Radboud University Nijmegen Medical Centre,
                     P. O. Box 9101, 6500 HB Nijmegen, The Netherlands.
SOURCE:              The Journal of biological chemistry, (2006 Jun 9) Vol. 281,
                     No. 23, pp. 15893-9.  Electronic Publication: 2006-03-24.
                     Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200608
ENTRY DATE:          Entered STN: 6 Jun 2006
                     Last Updated on STN: 24 Aug 2006
                     Entered Medline: 23 Aug 2006
AB   Cystatin M/E is a high affinity inhibitor of the asparaginyl
     endopeptidase legumain, and we have previously reported that both
     proteins are likely to be involved in the regulation of stratum corneum
     formation in skin.  Although cystatin M/E contains a predicted binding
     site for papain-like cysteine proteases, no high affinity binding for any
     member of this family has been demonstrated so far.  We report that human
     cathepsin V (CTSV) and human cathepsin L (CTSL) are strongly inhibited by
     human cystatin M/E.  Kinetic studies show that Ki values of cystatin M/E
     for the interaction with CTSV and CTSL are 0.47 and 1.78 nM, respectively.
     On the basis of the analogous sites in cystatin C, we
     used site-directed mutagenesis to identify the binding sites of these
     proteases in cystatin M/E.  We found that the W135A mutant was rendered
     inactive against CTSV and CTSL but retained legumain-inhibiting activity.
     Conversely, the N64A mutant lost legumain-inhibiting activity but remained
     active against the papain-like cysteine proteases.  We conclude that
     legumain and papain-like cysteine proteases are inhibited by two distinct
     non-overlapping sites.  Using immunohistochemistry on normal human skin,
     we found that cystatin M/E co-localizes with CTSV and CTSL.  In addition,
     we show that CTSL is the elusive enzyme that processes and activates
     epidermal transglutaminase 3.  The identification of CTSV and CTSL as
     novel targets for cystatin M/E, their (co)-expression in the stratum
     granulosum of human skin, and the activity of CTSL toward transglutaminase
     3 strongly imply an important role for these enzymes in the
     differentiation process of human epidermis.

L4   ANSWER 2 OF 9  SCISEARCH  COPYRIGHT (c) 2009 The Thomson Corporation  on
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STN
ACCESSION NUMBER: 2005:709440 SCISEARCH
THE GENUINE ARTICLE: 942VB
TITLE: Different cysteine proteinases involved in bone resorption and osteoclast formation
AUTHOR: Lerner U H (Reprint)
CORPORATE SOURCE: Umea Univ, Dept Oral Cell Biol, S-90187 Umea, Sweden (Reprint)
AUTHOR: Brage M; Abrahamson M; Lindstrom V; Grubb A
CORPORATE SOURCE: Lund Univ, Inst Lab Med, Dept Clin Chem, S-22185 Lund, Sweden
E-mail: ulf.lerner@odont.umu.se
COUNTRY OF AUTHOR: Sweden
SOURCE: CALCIFIED TISSUE INTERNATIONAL, (JUN 2005) Vol. 76, No. 6, pp. 439-447.
ISSN: 0171-967X.
PUBLISHER: SPRINGER, 233 SPRING STREET, NEW YORK, NY 10013 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 57
ENTRY DATE: Entered STN: 22 Jul 2005
Last Updated on STN: 20 Oct 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cysteine proteinases, especially cathepsin K, play an important role in osteoclastic degradation of bone matrix proteins and the process can, consequently, be significantly inhibited by cysteine proteinase inhibitors. We have recently reported that cystatin C and other cysteine proteinase inhibitors also reduce osteoclast formation. However, it is not known which cysteine proteinase(s) are involved in osteoclast differentiation. In the present study, we compared the relative potencies of cystatins C and D as inhibitors of bone resorption in cultured mouse calvariae, osteoclastogenesis in mouse bone marrow cultures, and cathepsin K activity. Inhibition of cathepsin K activity was assessed by determining equilibrium constants for inhibitor complexes in fluorogenic substrate assays. The data demonstrate that whereas human cystatins C and D are equipotent as inhibitors of bone resorption, cystatin D is 10-fold less potent as an inhibitor of osteoclastogenesis and 200-fold less potent as an inhibitor of cathepsin K activity. A recombinant human cystatin C variant with Gly substitutions for residues Arg(8), Leu(9), Val(10), and Trp(106) did not inhibit bone resorption, had 1,000-fold decreased inhibitory effect on catbepsin K activity compared to wildtype cystatin C, but was equipotent with wildtype cystatin C as an inhibitor of osteoclastogenesis. It is concluded that (i) different cysteine proteinases are likely to be involved in bone resorption and osteoclast formation, (ii) cathepsin K may not be an exclusive target enzyme in any of the two systems, and (iii) the enzyme(s) involved in osteoclastogenesis might not be a typical papain-like cysteine proteinase.

L4 ANSWER 3 OF 9 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:501782 SCISEARCH
THE GENUINE ARTICLE: 686WD
TITLE: Overexpression of legumain in tumors is significant for invasion/metastasis and a candidate enzymatic target for prodrug therapy
AUTHOR: Liu C (Reprint)
CORPORATE SOURCE: Scripps Res Inst, Dept Immunol, 10666 N Torrey Pines Rd, La Jolla, CA 92037 USA (Reprint)
AUTHOR: Sun C Z; Huang H N; Janda K; Edgington T
CORPORATE SOURCE: Scripps Res Inst, Dept Immunol, La Jolla, CA 92037 USA; Scripps Res Inst, Dept Chem, La Jolla, CA 92037 USA

COUNTRY OF AUTHOR: USA
SOURCE: CANCER RESEARCH, (1 JUN 2003) Vol. 63, No. 11, pp. 2957-2964.
ISSN: 0008-5472.
PUBLISHER: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 39
ENTRY DATE: Entered STN: 3 Jul 2003
Last Updated on STN: 3 Jul 2003
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Expression of legumain, a novel asparaginyl endopeptidase, in tumors was identified from gene expression profiling and tumor tissue array analysis. Legumain was demonstrated in membrane-associated vesicles concentrated at the invadopodia of tumor cells and on cell surfaces where it colocalized with integrins. Legumain was demonstrated to activate progelatinase A. Cells overexpressing legumain possessed increased migratory and invasive activity in vitro and adopted an invasive and metastatic phenotype in vivo, inferring significance of legumain in tumor invasion and metastasis. A prodrug strategy incorporating a legumain-cleavable peptide substrate onto doxorubicin was developed. The prototype compound, designated legubicin, exhibited reduced toxicity and was effectively tumoricidal in vivo in a murine colon carcinoma model.

L4 ANSWER 4 OF 9 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003374083 EMBASE
TITLE: Novel cell-permeable acyloxymethylketone inhibitors of asparaginyl endopeptidase.
AUTHOR: Loak, Kylie; Billson, Jeremy; Morton, Fraser; Hewitt, Ellen
CORPORATE SOURCE: Medivir UK Ltd., 100 Fulbourn Road, Cambridge CB1 9PT, United Kingdom.
AUTHOR: Li, Dongtao Ni; Manoury, Benedicte; Watts, Colin (correspondence)
CORPORATE SOURCE: Division of Cell Biology/Immunology, School of Life Science, University of Dundee, Dundee DD1 4HN, United Kingdom.
SOURCE: Biological Chemistry, (1 Aug 2003) Vol. 384, No. 8, pp. 1239-1246.
Refs: 25
ISSN: 1431-6730 CODEN: BICHF3
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 2003
Last Updated on STN: 2 Oct 2003

AB Mammalian asparaginyl endopeptidase (AEP) or legumain is a recently identified lysosomal cysteine protease belonging to clan CD. To date it has been shown to be involved in antigen presentation within class II MHC positive cells and in pro-protein processing. Further elucidation of the biological functions of the enzyme will require potent and selective inhibitors and thus we describe here new acyloxymethylketone inhibitors of AEP. The most potent of the series is 2,6-dimethyl-benzoic acid 3-benzyloxycarbonylamino-4-carbamoyl-2-oxo-butyl ester (MV026630) with a k(obs)/[I] value of 1.09x10(5) M(-1)s(-1). At low μm concentrations this compound is able to enter living cells and

irreversibly inactivate AEP. We show that this results in inhibition of AEP autoactivation and in perturbation of the processing and presentation of T cell epitopes from both tetanus toxin and myelin basic protein.

L4 ANSWER 5 OF 9 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:900907 SCISEARCH
THE GENUINE ARTICLE: 589BH
TITLE: Inhibition of mammalian legumain by Michael acceptors and AzaAsn-halomethylketones
AUTHOR: Demuth H U (Reprint)
CORPORATE SOURCE: Probiodrug AG, Weinbergweg 22 Bioctr, D-06120 Halle Saale, Germany (Reprint)
AUTHOR: Niestroj A J; Feussner K; Heiser U; Dando P M; Barrett A; Gerhartz B
CORPORATE SOURCE: Probiodrug AG, D-06120 Halle Saale, Germany; Babraham Inst, MRC, Mol Enzymol Lab, Cambridge CB2 4AT, England
COUNTRY OF AUTHOR: Germany; England
SOURCE: BIOLOGICAL CHEMISTRY, (JUL-AUG 2002) Vol. 383, No. 7-8, pp. 1205-1214.
ISSN: 1431-6730.
PUBLISHER: WALTER DE GRUYTER & CO, GENTHINER STRASSE 13, D-10785 BERLIN, GERMANY.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 38
ENTRY DATE: Entered STN: 26 Nov 2002
Last Updated on STN: 26 Nov 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Legumain is a lysosomal cysteine peptidase specific for an asparagine residue in the P-1-position. It has been classified as a member of clan CD peptidases due to predicted structural similarities to caspases and gingipains. So far, inhibition studies on legumain are limited by the use of endogenous inhibitors such as cystatin C. A series of Michael acceptor inhibitors based on the backbone CbzLAlaLAlaLAsn (Cbz= benzyloxycarbonyl) has been prepared and resulted in an irreversible inhibition of porcine legumain. Variation of the molecular size within the war head revealed the best inhibition for the compound containing the allyl ester (k(obs)/I=766 M(-1)s(-1)). To overcome cyclisation between the amide moiety of the Asn residue and the war head, several asparagine analogues have been synthesised. Integrated in halomethylketone inhibitors, azaasparagine is accepted by legumain in the P-1-position. The most potent inhibitor of this series, CbzLAlaLAlaAzaAsnchloromethylketone, displays a k(obs)/I value of 139 000 M(-1)s(-1). Other cysteine peptidases, such as papain and cathepsin B, are not inhibited by this compound at concentrations up to 100 muM. The synthetic inhibitors described here represent useful tools for the investigation of the structural and physiological properties of this unique asparaginespecific peptidase.

L4 ANSWER 6 OF 9 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:463594 SCISEARCH
THE GENUINE ARTICLE: 438WE
TITLE: Bm-CPI-2, a cystatin homolog secreted by the filarial parasite Brugia malayi, inhibits class II MHC-restricted antigen processing
AUTHOR: Watts C (Reprint)
CORPORATE SOURCE: Univ Dundee, Dept Biochem, Wellcome Trust Bioctr, Dundee DD1 5EH, Scotland (Reprint)
AUTHOR: Manoury B; Gregory W F; Maizels R M
CORPORATE SOURCE: Univ Edinburgh, Inst Cell Anim & Populat Biol, Edinburgh

EH9 3JT, Midlothian, Scotland
COUNTRY OF AUTHOR: Scotland
SOURCE: CURRENT BIOLOGY, (20 MAR 2001) Vol. 11, No. 6, pp. 447-451
.
ISSN: 0960-9822.
PUBLISHER: CELL PRESS, 1100 MASSACHUSETTES AVE,, CAMBRIDGE, MA 02138 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 24
ENTRY DATE: Entered STN: 22 Jun 2001
Last Updated on STN: 22 Jun 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB While interference with the class I MHC pathway by pathogen-encoded gene products, especially those of viruses, has been well documented, few examples of specific interference with the MHC class II pathway have been reported, Potential targets for such interference are the proteases that remove the invariant chain chaperone and generate antigenic peptides, Indeed, recent studies indicate that immature dendritic cells express cystatin C to modulate cysteine protease activity and the expression of class II MHC molecules [1], Here, we show that Bm-CPI-2, a recently discovered cystatin homolog produced by the filarial nematode parasite Brugia malayi (W, F. Gregory et al,, submitted), inhibits multiple cysteine protease activities found in the endosomes/lysosomes of human a lymphocyte lines. CPI-2 blocked the hydrolysis of synthetic substrates favored by two different families of lysosomal cysteine proteases and blocked the in vitro processing of the tetanus toxin antigen by purified lysosome fractions. Moreover, CPI-2 substantially inhibited the presentation of selected T cell epitopes from tetanus toxin by living antigen-presenting cells. Our studies provide the first example of a product from a eukaryotic parasite that can directly interfere with antigen presentation, which, in turn, may suggest how filarial parasites might inactivate the host immune response to a helminth invader.

L4 ANSWER 7 OF 9 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:500697 SCISEARCH
THE GENUINE ARTICLE: 212BK
TITLE: Inhibition of mammalian legumain by some cystatins is due to a novel second reactive site
AUTHOR: Abrahamson M (Reprint)
CORPORATE SOURCE: Univ Lund Hosp, Inst Lab Med, Dept Clin Chem, S-22185 Lund, Sweden (Reprint)
AUTHOR: Alvarez-Fernandez M; Barrett A J; Gerhartz B; Dando P M; Ni J A
CORPORATE SOURCE: Babraham Inst, MRC, Mol Enzymol Lab, Cambridge CB2 4AT, England; Human Genome Sci Inc, Rockville, MD 20850 USA
COUNTRY OF AUTHOR: Sweden; England; USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2 JUL 1999) Vol. 274, No. 27, pp. 19195-19203.
ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 55
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have investigated the inhibition of the recently identified family C13 cysteine peptidase, pig legumain, by human cystatin C, The cystatin was seen to inhibit enzyme activity by

stoichiometric 1:1 binding in competition with substrate. The K-i value for the interaction was 0.20 nM, i.e. cystatin C had an affinity for legumain similar to that for the papain-like family C1 cysteine peptidase, cathepsin B, However, cystatin C variants with alterations in the N-terminal region and the "second hairpin loop" that rendered the cystatin inactive against cathepsin B, still inhibited legumain with K-i values 0.2-0.3 nM. Complexes between cystatin C and papain inhibited legumain activity against benzoyl-Asn-NHPhNO2, as efficiently as did cystatin C alone, Conversely, cystatin C inhibited papain activity against benzoyl-Arg-NHPhNO2 whether or not the cystatin had been incubated with legumain, strongly indicating that the cystatin inhibited the two enzymes with non-overlapping sites. A ternary complex between legumain, cystatin C, and papain was demonstrated by gel filtration supported by immunoblotting. Screening of a panel of cystatin superfamily members showed that type 1 inhibitors (cystatins A and B) and low M-r kininogen (type 3) did not inhibit pig legumain, Of human type 2 cystatins, cystatin D was non-inhibitory, whereas cystatin E/M and cystatin F displayed strong (K-i 0.0016 nM) and relatively weak (K-i 10 nM) affinity for legumain, respectively. Sequence alignments and molecular modeling led to the suggestion that a loop located on the opposite side to the papain-binding surface, between the alpha-helix and the first strand of the main beta-pleated sheet of the cystatin structure, could be involved in legumain binding. This was corroborated by analysis of a cystatin C variant with substitution of the Asn(39) residue in this loop (N39K-cystatin C); this variant showed a slight reduction in affinity for cathepsin B (K-i 1.5 nM) but much greater than 5,000-fold lower affinity for legumain (K-i much greater than 1,000 nM) than wild-type cystatin C.

L4 ANSWER 8 OF 9 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:713452 SCISEARCH
THE GENUINE ARTICLE: 238MA
TITLE: Colorimetric and fluorimetric microplate assays for legumain and a staining reaction for detection of the enzyme after electrophoresis
AUTHOR: Barrett A J (Reprint)
CORPORATE SOURCE: Babraham Inst, Mol Enzymol Lab, MRC, Babraham CB2 4AT, Cambs, England (Reprint)
AUTHOR: Johansen H T; Knight C G
CORPORATE SOURCE: Univ Cambridge, Dept Biochem, Cambridge CB2 1QW, England; Univ Oslo, Sch Pharm, N-0316 Oslo, Norway
COUNTRY OF AUTHOR: England; Norway
SOURCE: ANALYTICAL BIOCHEMISTRY, (10 SEP 1999) Vol. 273, No. 2, pp. 278-283.
ISSN: 0003-2697.
PUBLISHER: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 19
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The cysteine endopeptidase legumain was recently discovered in mammalian cells, predominantly localized in the lysosomal system where it is believed to contribute to antigen processing for MHC class II. Here we describe rapid assay procedures for the enzyme in 96-well microplates with two substrates, a novel compound, succinyl-Ala-Ala-Asn-4-methoxy-2-naphthylamide, and benzyloxycarbonyl-Ala-Ala-Asn-4-methyl-7-coumarylamide.

Both substrates are suitable for fluorimetric assays, but the naphthylamide also allows colorimetric detection of legumain activity, since the released 4-methoxy-2-naphthylamine gives a red product when coupled with the Fast Garnet color reagent. We show that the naphthylamide substrate can be used to visualize active legumain after electrophoresis in polyacrylamide gel. Both substrates provide assays that are reproducible and sufficiently sensitive to allow the assay of legumain in crude samples such as tissue homogenates, although the coumarylamide is the more sensitive. The specificity of both assay methods for legumain was verified by the lack of inhibition by E-64 and total inhibition by eggwhite cystatin. (C) 1999 Academic Press.

L4 ANSWER 9 OF 9 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 1997218252 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9065484
TITLE: Cloning, isolation, and characterization of mammalian legumain, an asparaginyl endopeptidase.
AUTHOR: Chen J M; Dando P M; Rawlings N D; Brown M A; Young N E; Stevens R A; Hewitt E; Watts C; Barrett A J
CORPORATE SOURCE: Medical Research Council Peptidase Laboratory, Department of Immunology, The Babraham Institute, Babraham Hall, Babraham, Cambridgeshire CB2 4AT, United Kingdom.
SOURCE: The Journal of biological chemistry, (1997 Mar 21) Vol. 272, No. 12, pp. 8090-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-Y09862
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 6 May 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 18 Apr 1997

AB Legumain is a cysteine endopeptidase that shows strict specificity for hydrolysis of asparaginyl bonds. The enzyme belongs to peptidase family C13, and is thus unrelated to the better known cysteine peptidases of the papain family, C1 (Rawlings, N. D., and Barrett, A. J. (1994) Methods Enzymol. 244, 461-486). To date, legumain has been described only from plants and a blood fluke, Schistosoma mansoni. We now show that legumain is present in mammals. We have cloned and sequenced human legumain and part of pig legumain. We have also purified legumain to homogeneity (2200-fold, 8% yield) from pig kidney. The mammalian sequences are clearly homologous with legumains from non-mammalian species. Pig legumain is a glycoprotein of about 34 kDa, decreasing to 31 kDa on deglycosylation. It is an asparaginyl endopeptidase, hydrolyzing Z-Ala-Ala-Asn-7-(4-methyl)coumarylamide and benzoyl-Asn-p-nitroanilide. Maximal activity is seen at pH 5.8 under normal assay conditions, and the enzyme is irreversibly denatured at pH 7 and above. Mammalian legumain is a cysteine endopeptidase, inhibited by iodoacetamide and maleimides, but unaffected by compound E64 (trans-epoxysuccinyl-L-leucylamido-(4-guanidino)butane). It is inhibited by ovocystatin (cystatin from chicken egg white) and human cystatin C with Ki values < 5 nM. We discuss the significance of the discovery of a cysteine endopeptidase of a new family and distinctive specificity in man and other mammals.

=> s legumain
L5 331 LEGUMAIN

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=> s l2 and l5
L6          28 L2 AND L5

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7           17 DUP REM L6 (11 DUPLICATES REMOVED)

=> d ibib abs 1-17

L7   ANSWER 1 OF 17     MEDLINE on STN                  DUPLICATE 1
ACCESSION NUMBER:   2008344992     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 18508595
TITLE:              Cystatins: biochemical and structural properties, and
                    medical relevance.
AUTHOR:             Turk Vito; Stoka Veronika; Turk Dusan
CORPORATE SOURCE:   J. Stefan Institute, Dept. of Biochemistry, Molecular and
                    Structural Biology, SI-1000 Ljubljana, Slovenia..
                    vito.turk@ijs.si
SOURCE:             Frontiers in bioscience : a journal and virtual library,
                    (2008) Vol. 13, pp. 5406-20.  Electronic Publication:
                    2008-05-01. Ref: 163
                    Journal code: 9709506. E-ISSN: 1093-4715.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
                    (RESEARCH SUPPORT, NON-U.S. GOV'T)
                    General Review; (REVIEW)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200809
ENTRY DATE:         Entered STN: 30 May 2008
                    Last Updated on STN: 20 Sep 2008
                    Entered Medline: 19 Sep 2008
AB   The cystatin superfamily comprises a large group of the cystatin domain
     containing proteins, present in a wide variety of organisms, including
     humans.  Cystatin inhibitory activity is vital for the delicate regulation
     of normal physiological processes by limiting the potentially highly
     destructive activity of their target proteases such as the papain (C1)
     family, including cysteine cathepsins.  Some of the cystatins also inhibit
     the legumain (C13) family of enzymes.  Failures in biological
     mechanisms controlling protease activities result in many diseases such as
     neurodegeneration, cardiovascular diseases, osteoporosis, arthritis, and
     cancer.  Cystatins have been classified into three types: the stefins, the
     cystatins and the kininogens, although other cystatin-related proteins,
     such as CRES proteins, are emerging.  The stefins are mainly intracellular
     proteins, whereas the cystatins and the kininogens are extracellular.  The
     cystatins are tight binding and reversible inhibitors.  The basic
     mechanism of interaction between cystatins and their target proteases has
     been established, based mainly on the crystal structures of various
     cathepsins, stefins and cystatins and their enzyme-inhibitor complexes.
     Cystatins, as rather non-selective inhibitors, discriminate only slightly
     between endo- and exopeptidases.  They are also prone to form amyloids.
     The levels of some stefins and cystatins in tissue and body fluids can
     serve as relatively reliable markers for a variety of diseases.  In this
     review we summarize present knowledge about cystatins and their role in
     some diseases.

L7   ANSWER 2 OF 17  EMBASE  COPYRIGHT (c) 2009 Elsevier B.V. All rights
     reserved on STN
ACCESSION NUMBER:   2008510229  EMBASE
TITLE:              Metadegradomics: Toward in vivo quantitative degradomics of
                    proteolytic post-translational modifications of the cancer
                    proteome.
```

AUTHOR: Doucet, Alain (correspondence); Butler, Georgina S.; Rodriguez, David; Prudova, Anna; Overall, Christopher M.
CORPORATE SOURCE: Centre for Blood Research, 4.401 Life Sciences Institute, University of British Columbia, 2350 Health Sciences Mall, Vancouver, BC V6T 1Z3, Canada. adoucet@interchange.ubc.ca; chris.overall@ubc.ca
SOURCE: Molecular and Cellular Proteomics, (October 2008) Vol. 7, No. 10, pp. 1925-1951.
Refs: 206
ISSN: 1535-9476 CODEN: MCPOBS
PUBLISHER: American Society for Biochemistry and Molecular Biology Inc., 9650 Rockville Pike, Bethesda, MD 20814, United States.
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 28 Nov 2008
Last Updated on STN: 28 Nov 2008

AB Post-translational modifications enable extra layers of control of the proteome, and perhaps the most important is proteolysis, a major irreversible modification affecting every protein. The intersection of the protease web with a proteome sculpts that proteome, dynamically modifying its state and function. Protease expression is distorted in cancer, so perturbing signaling pathways and the secretome of the tumor and reactive stromal cells. Indeed many cancer biomarkers are stable proteolytic fragments. It is crucial to determine which proteases contribute to the pathology versus their roles in homeostasis and in mitigating cancer. Thus the full substrate repertoire of a protease, termed the substrate degradome, must be deciphered to define protease function and to identify drug targets. Degradomics has been used to identify many substrates of matrix metalloproteinases that are important proteases in cancer. Here we review recent degradomics technologies that allow for the broadly applicable identification and quantification of proteases (the protease degradome) and their activity state, substrates, and interactors. Quantitative proteomics using stable isotope labeling, such as ICAT, isobaric tags for relative and absolute quantification (iTRAQ), and stable isotope labeling by amino acids in cell culture (SILAC), can reveal protease substrates by taking advantage of the natural compartmentalization of membrane proteins that are shed into the extracellular space. Identifying the actual cleavage sites in a complex proteome relies on positional proteomics and utilizes selection strategies to enrich for protease-generated neo-N termini of proteins. In so doing, important functional information is generated. Finally protease substrates and interactors can be identified by interactomics based on affinity purification of protease complexes using exosite scanning and inactive catalytic domain capture strategies followed by mass spectrometry analysis. At the global level, the N terminome analysis of whole communities of proteases in tissues and organs in vivo provides a full scale understanding of the protease web and the web-sculpted proteome, so defining metadegradomics. .COPYRGT. 2008 by The American Society for Biochemistry and Molecular Biology, Inc.

L7 ANSWER 3 OF 17 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2007384714 EMBASE
TITLE: Tumor immunoediting and immunosculpting pathways to cancer progression.
AUTHOR: Reiman, Jennifer M.; Knutson, Keith L. (correspondence)
CORPORATE SOURCE: Department of Immunology, Mayo Clinic College of Medicine,

200 First Street SW, Rochester, MN 55905, United States. knutson.keith@mayo.edu
AUTHOR: Kmieciak, Maciej; Manjili, Masoud H.
CORPORATE SOURCE: Department of Microbiology and Immunology, VCU School of Medicine, Massey Cancer Center, Richmond, VA 23298, United States.
SOURCE: Seminars in Cancer Biology, (Aug 2007) Vol. 17, No. 4, pp. 275-287.
Refs: 149
ISSN: 1044-579X CODEN: SECBE7
PUBLISHER IDENT.: S 1044-579X(07)00034-X
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Sep 2007
Last Updated on STN: 4 Sep 2007

AB Recent studies have suggested that a natural function of the immune system is to respond and destroy aberrant, dysfunctional cells by a process called immunosurveillance. These studies also suggest that the tumors that arise despite immunosurveillance have been immunosculpted by the immune system. The purported abilities of tumors to induce immune tolerance and suppression, the increased pathogenic behavior of the tumor cells following exposure to immune effectors and the loss of immunogenicity (i.e. immunoediting) often observed in advanced stage tumors could be the result of immunosculpting. In some cases, these immunosculpting features may be permanent and irreversible. However, in other cases, reversible epigenetic mechanisms may underlie the immune resistant tumor phenotype. Regardless, these immune-induced alterations could contribute to cancer pathogenesis. Understanding the mechanisms by which tumors evade immunity will be important for disease prevention and therapeutics.

L7 ANSWER 4 OF 17 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2006331066 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16565075
TITLE: Cystatin M/E is a high affinity inhibitor of cathepsin V and cathepsin L by a reactive site that is distinct from the legumain-binding site. A novel clue for the role of cystatin M/E in epidermal cornification.
AUTHOR: Cheng Tsing; Hitomi Kiyotaka; van Vlijmen-Willems Ivonne M J J; de Jongh Gys J; Yamamoto Kanae; Nishi Koji; Watts Colin; Reinheckel Thomas; Schalkwijk Joost; Zeeuwen Patrick L J M
CORPORATE SOURCE: Department of Dermatology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, P. O. Box 9101, 6500 HB Nijmegen, The Netherlands.
SOURCE: The Journal of biological chemistry, (2006 Jun 9) Vol. 281, No. 23, pp. 15893-9. Electronic Publication: 2006-03-24.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200608
ENTRY DATE: Entered STN: 6 Jun 2006

Last Updated on STN: 24 Aug 2006
Entered Medline: 23 Aug 2006

AB Cystatin M/E is a high affinity inhibitor of the asparaginyl endopeptidase legumain, and we have previously reported that both proteins are likely to be involved in the regulation of stratum corneum formation in skin. Although cystatin M/E contains a predicted binding site for papain-like cysteine proteases, no high affinity binding for any member of this family has been demonstrated so far. We report that human cathepsin V (CTSV) and human cathepsin L (CTSL) are strongly inhibited by human cystatin M/E. Kinetic studies show that Ki values of cystatin M/E for the interaction with CTSV and CTSL are 0.47 and 1.78 nM, respectively. On the basis of the analogous sites in cystatin C, we used site-directed mutagenesis to identify the binding sites of these proteases in cystatin M/E. We found that the W135A mutant was rendered inactive against CTSV and CTSL but retained legumain-inhibiting activity. Conversely, the N64A mutant lost legumain-inhibiting activity but remained active against the papain-like cysteine proteases. We conclude that legumain and papain-like cysteine proteases are inhibited by two distinct non-overlapping sites. Using immunohistochemistry on normal human skin, we found that cystatin M/E co-localizes with CTSV and CTSL. In addition, we show that CTSL is the elusive enzyme that processes and activates epidermal transglutaminase 3. The identification of CTSV and CTSL as novel targets for cystatin M/E, their (co)-expression in the stratum granulosum of human skin, and the activity of CTSL toward transglutaminase 3 strongly imply an important role for these enzymes in the differentiation process of human epidermis.

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ACCESSION NUMBER: 2005198390 EMBASE
TITLE: The human brain mannose 6-phosphate glycoproteome: A complex mixture composed of multiple isoforms of many soluble lysosomal proteins.
AUTHOR: Sleat, David E.; Lackland, Henry; Wang, Yanhong; Sohar, Istvan; Xiao, Gang; Lobel, Peter, Dr. (correspondence)
CORPORATE SOURCE: Ctr. for Adv. Biotech. and Medicine, Univ. of Med./Dent. of New Jersey, Piscataway, NJ, United States. sleat@cabm.rutgers.edu; lobel@cabm.rutgers.edu
AUTHOR: Sleat, David E.; Lobel, Peter, Dr. (correspondence)
CORPORATE SOURCE: Department of Pharmacology, Univ. of Med./Dent. of New Jersey, Piscataway, NJ, United States. sleat@cabm.rutgers.edu; lobel@cabm.rutgers.edu
AUTHOR: Li, Hong
CORPORATE SOURCE: Dept. of Biochem. and Molec. Biology, New Jersey Medical School, Newark, NJ, United States.
AUTHOR: Lobel, Peter, Dr. (correspondence)
CORPORATE SOURCE: Ctr. for Adv. Biotech. and Medicine, 679 Hoes Lane, Piscataway, NJ 08854, United States. lobel@cabm.rutgers.edu
AUTHOR: Xiao, Gang
CORPORATE SOURCE: Genomics Institute, University of Pennsylvania, Philadelphia, PA 10104, United States.
SOURCE: Proteomics, (Apr 2005) Vol. 5, No. 6, pp. 1520-1532.
Refs: 41
ISSN: 1615-9853 CODEN: PROTC7
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 May 2005
Last Updated on STN: 26 May 2005

AB The lysosome is a membrane delimited cytoplasmic organelle that contains

at least 50 hydrolytic enzymes and associated cofactors. The biomedical importance of these enzymes is highlighted by the many lysosomal storage disorders that are associated with mutations in genes encoding lysosomal proteins, and there is also evidence that lysosomal activities may be involved in more widespread human diseases. The aim of this study was to characterize the human brain lysosomal proteome with the goal of establishing a reference map to investigate human diseases of unknown etiology and to gain insights into the cellular function of the lysosome. Proteins containing mannose 6-phosphate (Man6-P), a carbohydrate modification used for targeting resident soluble lysosomal proteins to the lysosome, were affinity-purified using immobilized Man6-P receptor. Fractionation by two-dimensional electrophoresis resolved a complex mixture comprising approximately 800 spots. Constituent proteins in each spot were identified using a combination of matrix-assisted laser desorption/ionization- time of flight mass spectrometry (both mass spectrometry (MS/MS) and tandem peptide mass fingerprinting) on in-gel tryptic digests and N-terminal sequencing. In a complementary analysis, we also analyzed a tryptic digest of the unfractionated mixture by liquid chromatography MS/MS. In total, 61 different proteins were identified. Seven were likely contaminants associated with true Man6-P glycoproteins. Forty-one were known lysosomal proteins of which 11 have not previously been reported to contain Man6-P. An additional nine proteins were either uncharacterized or proteins not previously reported to have lysosomal function. We found that the human brain Man6-P-containing lysosomal proteome is highly complex and contains more proteins with a much greater number of individual isoforms than found in previous studies of Man6-P glycoproteomes. .COPYRGT. 2005 WILEY-VCH Verlag GmbH & Co. KGaA.

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ACCESSION NUMBER: 2005166543 EMBASE
TITLE: Proteinaceous cysteine protease inhibitors.
AUTHOR: Dubin, G. (correspondence)
CORPORATE SOURCE: Faculty of Biotechnology, Jagiellonian University, ul. Gronostajowa 7, 30-387 Krakow, Poland. gdubin@mol.uj.edu.pl
SOURCE: Cellular and Molecular Life Sciences, (Mar 2005) Vol. 62, No. 6, pp. 653-669.
Refs: 151
ISSN: 1420-682X CODEN: CMLSFI
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 28 Apr 2005
Last Updated on STN: 28 Apr 2005

AB Studies of proteinaceous cysteine protease inhibitors originated with the discovery of cystatins in the 1960s. Since that time, a rich and fascinating world of proteins that control and regulate a multitude of important physiological processes, ranging from the basics of protein turnover to development and brain function, has been uncovered. Failures in such important and complex systems inevitably lead to pathologies. Many threatening diseases such as cancer or neurological disorders, to mention only some, are attributed to deregulation of protease-inhibitor balance. Moreover, important aspects of infection pathology and host defense rely on proteolysis and protease inhibition. Recent advances in the field of protease inhibitors have drawn attention to the possible use of this collected knowledge to control related pathological processes. This review attempts to familiarize the reader with proteinaceous cysteine protease inhibitors by providing an overview of current knowledge. The work primarily highlights biological processes in which the inhibitors are involved and focuses on pathologies resulting from aberrant

protease-inhibitor balance, pointing out emerging possibilities for their correction. .COPYRGT. Birkhauser Verlag, Basel, 2005.

L7 ANSWER 7 OF 17 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2005315727 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15614539
TITLE: Cystatin C uptake in the eye.
AUTHOR: Wasselius Johan; Johansson Kjell; Hakansson Katarina; Abrahamson Magnus; Ehinger Berndt
CORPORATE SOURCE: Department of Ophthalmology, University Hospital, Lund University, 221 85, Lund, Sweden,. Berndt.Ehinger@oft.lu.se
SOURCE: Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie, (2005 Jun) Vol. 243, No. 6, pp. 583-92. Electronic Publication: 2004-12-22. Journal code: 8205248. ISSN: 0721-832X.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 21 Jun 2005
Last Updated on STN: 14 Dec 2005
AB BACKGROUND: As a secreted protein, cystatin C is assumed to play its role in the extracellular compartment, where it can inhibit virtually all cysteine proteases of families C1 (cathepsin B, L, S) and C13 (mammalian legumain-related proteases). Since many of its potential target enzymes in the eye reside in intracellular compartments, we sought evidence for a cellular uptake of the inhibitor in ocular tissues. METHODS: Fluorescence-labeled human cystatin C was injected intravitreally into normal rat eyes. Ocular tissues were subsequently examined using ELISA, fluorescence microscopy, and immunohistochemistry. Cystatin C uptake was additionally studied in an in vitro retina model. RESULTS: Cystatin C administered intravitreally in vivo is taken up into cells of the corneal endothelium and epithelium, the epithelial cells lining the ciliary processes, and into cells in the neuroretina (mostly ganglion cells) and the retinal pigment epithelium. The uptake is demonstrable also in vitro and was, in the neuroretina, found to be a high-affinity system, inhibited by cooling the specimens or by adding the microfilament polymerization inhibitor, cytochalasin D, to the medium. CONCLUSIONS: There is an active, temperature-dependent uptake system for cystatin C into several cell types in the cornea, ciliary body, and retina. The cell types that take up cystatin C are generally the same that contain endogenous cystatin C, suggesting that much or all cystatin C seen intracellularly in the normal eye may have been taken up from the surrounding extracellular space. The uptake indicates that the inhibitor may exert biological functions in intracellular compartments. It is also possible that this uptake system may regulate the extracellular levels of cystatin C in the eye.

L7 ANSWER 8 OF 17 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:709440 SCISEARCH
THE GENUINE ARTICLE: 942VB
TITLE: Different cysteine proteinases involved in bone resorption and osteoclast formation
AUTHOR: Lerner U H (Reprint)
CORPORATE SOURCE: Umea Univ, Dept Oral Cell Biol, S-90187 Umea, Sweden (Reprint)
AUTHOR: Brage M; Abrahamson M; Lindstrom V; Grubb A

CORPORATE SOURCE: Lund Univ, Inst Lab Med, Dept Clin Chem, S-22185 Lund, Sweden
E-mail: ulf.lerner@odont.umu.se
COUNTRY OF AUTHOR: Sweden
SOURCE: CALCIFIED TISSUE INTERNATIONAL, (JUN 2005) Vol. 76, No. 6, pp. 439-447.
ISSN: 0171-967X.
PUBLISHER: SPRINGER, 233 SPRING STREET, NEW YORK, NY 10013 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 57
ENTRY DATE: Entered STN: 22 Jul 2005
Last Updated on STN: 20 Oct 2005

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cysteine proteinases, especially cathepsin K, play an important role in osteoclastic degradation of bone matrix proteins and the process can, consequently, be significantly inhibited by cysteine proteinase inhibitors. We have recently reported that cystatin C and other cysteine proteinase inhibitors also reduce osteoclast formation. However, it is not known which cysteine proteinase(s) are involved in osteoclast differentiation. In the present study, we compared the relative potencies of cystatins C and D as inhibitors of bone resorption in cultured mouse calvariae, osteoclastogenesis in mouse bone marrow cultures, and cathepsin K activity. Inhibition of cathepsin K activity was assessed by determining equilibrium constants for inhibitor complexes in fluorogenic substrate assays. The data demonstrate that whereas human cystatins C and D are equipotent as inhibitors of bone resorption, cystatin D is 10-fold less potent as an inhibitor of osteoclastogenesis and 200-fold less potent as an inhibitor of cathepsin K activity. A recombinant human cystatin C variant with Gly substitutions for residues Arg(8), Leu(9), Val(10), and Trp(106) did not inhibit bone resorption, had 1,000-fold decreased inhibitory effect on catbepsin K activity compared to wildtype cystatin C, but was equipotent with wildtype cystatin C as an inhibitor of osteoclastogenesis. It is concluded that (i) different cysteine proteinases are likely to be involved in bone resorption and osteoclast formation, (ii) cathepsin K may not be an exclusive target enzyme in any of the two systems, and (iii) the enzyme(s) involved in osteoclastogenesis might not be a typical papain-like cysteine proteinase.

L7 ANSWER 9 OF 17 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:501782 SCISEARCH
THE GENUINE ARTICLE: 686WD
TITLE: Overexpression of legumain in tumors is significant for invasion/metastasis and a candidate enzymatic target for prodrug therapy
AUTHOR: Liu C (Reprint)
CORPORATE SOURCE: Scripps Res Inst, Dept Immunol, 10666 N Torrey Pines Rd, La Jolla, CA 92037 USA (Reprint)
AUTHOR: Sun C Z; Huang H N; Janda K; Edgington T
CORPORATE SOURCE: Scripps Res Inst, Dept Immunol, La Jolla, CA 92037 USA; Scripps Res Inst, Dept Chem, La Jolla, CA 92037 USA
COUNTRY OF AUTHOR: USA
SOURCE: CANCER RESEARCH, (1 JUN 2003) Vol. 63, No. 11, pp. 2957-2964.
ISSN: 0008-5472.
PUBLISHER: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 39

ENTRY DATE: Entered STN: 3 Jul 2003
Last Updated on STN: 3 Jul 2003
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Expression of legumain, a novel asparaginyl endopeptidase, in tumors was identified from gene expression profiling and tumor tissue array analysis. Legumain was demonstrated in membrane-associated vesicles concentrated at the invadopodia of tumor cells and on cell surfaces where it colocalized with integrins. Legumain was demonstrated to activate progelatinase A. Cells overexpressing legumain possessed increased migratory and invasive activity in vitro and adopted an invasive and metastatic phenotype in vivo, inferring significance of legumain in tumor invasion and metastasis. A prodrug strategy incorporating a legumain-cleavable peptide substrate onto doxorubicin was developed. The prototype compound, designated legubicin, exhibited reduced toxicity and was effectively tumoricidal in vivo in a murine colon carcinoma model.

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ACCESSION NUMBER: 2003374083 EMBASE
TITLE: Novel cell-permeable acyloxymethylketone inhibitors of asparaginyl endopeptidase.
AUTHOR: Loak, Kylie; Billson, Jeremy; Morton, Fraser; Hewitt, Ellen
CORPORATE SOURCE: Medivir UK Ltd., 100 Fulbourn Road, Cambridge CB1 9PT, United Kingdom.
AUTHOR: Li, Dongtao Ni; Manoury, Benedicte; Watts, Colin (correspondence)
CORPORATE SOURCE: Division of Cell Biology/Immunology, School of Life Science, University of Dundee, Dundee DD1 4HN, United Kingdom.
SOURCE: Biological Chemistry, (1 Aug 2003) Vol. 384, No. 8, pp. 1239-1246.
Refs: 25
ISSN: 1431-6730 CODEN: BICHF3
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 2003
Last Updated on STN: 2 Oct 2003

AB Mammalian asparaginyl endopeptidase (AEP) or legumain is a recently identified lysosomal cysteine protease belonging to clan CD. To date it has been shown to be involved in antigen presentation within class II MHC positive cells and in pro-protein processing. Further elucidation of the biological functions of the enzyme will require potent and selective inhibitors and thus we describe here new acyloxymethylketone inhibitors of AEP. The most potent of the series is 2,6-dimethyl-benzoic acid 3-benzyloxycarbonylamino-4-carbamoyl-2-oxo-butyl ester (MV026630) with a k(obs)/[I] value of 1.09x10(5) M(-1)s(-1). At low μm concentrations this compound is able to enter living cells and irreversibly inactivate AEP. We show that this results in inhibition of AEP autoactivation and in perturbation of the processing and presentation of T cell epitopes from both tetanus toxin and myelin basic protein.

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ACCESSION NUMBER: 2003:465778 SCISEARCH
THE GENUINE ARTICLE: 679TA

TITLE: Proteome analysis of secreted proteins during osteoclast differentiation using two different methods: Two-dimensional electrophoresis and isotope-coded affinity tags analysis with two-dimensional chromatography
AUTHOR: Kubota K (Reprint)
CORPORATE SOURCE: Sankyo Co Ltd, Biomed Res Labs, Shinagawa Ku, 1-2-58 Hiromachi, Tokyo 1408710, Japan (Reprint)
AUTHOR: Wakabayashi K; Matsuoka T
CORPORATE SOURCE: Sankyo Co Ltd, Biomed Res Labs, Shinagawa Ku, Tokyo 1408710, Japan; Sankyo Co Ltd, Lead Discovery Res Labs, Shinagawa Ku, Tokyo 1408710, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: PROTEOMICS, (MAY 2003) Vol. 3, No. 5, pp. 616-626. ISSN: 1615-9853.
PUBLISHER: WILEY-V C H VERLAG GMBH, PO BOX 10 11 61, D-69451 WEINHEIM, GERMANY.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 45
ENTRY DATE: Entered STN: 13 Jun 2003
Last Updated on STN: 13 Jun 2003
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Bone is maintained by two cell types, bone-forming osteoblasts and bone-resorbing osteoclasts. Osteoblasts express two factors, osteoprotegerin and receptor activator of NF-kappaB ligand (RANKL), inhibiting and promoting osteoclast differentiation, respectively. In contrast, modulators of bone resorption expressed by osteoclasts have not been so well studied enough. In the present study, we demonstrate proteome analysis of secreted proteins during osteoclast differentiation to elucidate the molecular mechanism of bone resorption and bone remodeling. To achieve this objective, we chose RAW264.7 cells with RANKL as a homogeneous osteoclast differentiation model and used two methods, two-dimensional gel electrophoresis (2-DE) and isotope-coded affinity tags (ICAT) analysis with two-dimensional liquid chromatography. We found 23 spots in 2-DE and 19 proteins in ICAT analysis which were expressed differently during osteoclast differentiation. These two methods gave us closely related but different information about proteins, suggesting they are complementary or at least supplementary methods at present. Cathepsins, osteopontin, legumain, macrophage inflammatory protein-1alpha, and other proteins were observed as up- or down-regulated proteins and are discussed in the context of osteoclast differentiation and bone resorption. In addition to confirming previous observations, this study indicates novel proteins related to osteoclast differentiation which are potential therapeutic targets for the treatment of bone diseases, such as osteoporosis.

L7 ANSWER 12 OF 17 MEDLINE on STN
ACCESSION NUMBER: 2003429788 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12970503
TITLE: Expression of sea anemone equistatin in potato. Effects of plant proteases on heterologous protein production.
AUTHOR: Outchkourov Nikolay S; Rogelj Boris; Strukelj Borut; Jongsma Maarten A
CORPORATE SOURCE: Plant Research International, P.O. Box 16, NL-6700 AA Wageningen, The Netherlands.
SOURCE: Plant physiology, (2003 Sep) Vol. 133, No. 1, pp. 379-90. Journal code: 0401224. ISSN: 0032-0889.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 13 Sep 2003
Last Updated on STN: 6 Jan 2004
Entered Medline: 5 Jan 2004

AB Plants are increasingly used as production platforms of various heterologous proteins, but rapid protein turnover can seriously limit the steady-state expression level. Little is known about specific plant proteases involved in this process. In an attempt to obtain potato (Solanum tuberosum cv Desiree) plants resistant to Colorado potato beetle (Leptinotarsa decemlineata Say) larvae, the protease inhibitor equistatin was expressed under the control of strong, light-inducible and constitutive promoters and was targeted to the secretory pathway with and without endoplasmic reticulum retention signal. All constructs yielded similar stepwise protein degradation patterns, which considerably reduced the amount of active inhibitor in planta and resulted in insufficient levels for resistance against Colorado potato beetle larvae. Affinity purification of the degradation products and N-terminal sequencing allowed the identification of the amino acid P(1)-positions (asparagine [Asn]-13, lysine-56, Asn-82, and arginine-151) that were cleaved in planta. The proteases involved in the equistatin degradation were characterized with synthetic substrates and inhibitors. Kininogen domain 3 completely inhibited equistatin degradation in vitro. The results indicate that arginine/lysine-specific and legumain-type Asn-specific cysteine proteases seriously impede the functional accumulation of recombinant equistatin in planta. General strategies to improve the resistance to proteases of heterologous proteins in plants are proposed.

L7 ANSWER 13 OF 17 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002676498 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12437107
TITLE: Inhibition of mammalian legumain by Michael acceptors and AzaAsn-halomethylketones.
AUTHOR: Niestroj Andre J; Feussner Kirstin; Heiser Ulrich; Dando Pam M; Barrett Alan; Gerhartz Bernd; Demuth Hans-Ulrich
CORPORATE SOURCE: Probiodrug AG, Biocenter, Halle, Saale, Germany.
SOURCE: Biological chemistry, (2002 Jul-Aug) Vol. 383, No. 7-8, pp. 1205-14.
Journal code: 9700112. ISSN: 1431-6730.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20 Nov 2002
Last Updated on STN: 15 Jul 2003
Entered Medline: 14 Jul 2003

AB Legumain is a lysosomal cysteine peptidase specific for an asparagine residue in the P1-position. It has been classified as a member of clan CD peptidases due to predicted structural similarities to caspases and gingipains. So far, inhibition studies on legumain are limited by the use of endogenous inhibitors such as cystatin C. A series of Michael acceptor inhibitors based on the backbone Cbz-L-Ala-L-Ala-L-Asn (Cbz= benzyloxycarbonyl) has been prepared and resulted in an irreversible inhibition of porcine legumain. Variation of the molecular size within the 'war head' revealed the best inhibition for the compound containing the allyl ester (kobs/I=766 M(-1) s(-1)). To overcome cyclisation between the amide moiety of the Asn residue and the 'war head', several asparagine analogues have been synthesised. Integrated in halomethylketone inhibitors, azaasparagine is accepted by legumain in the P1-position. The most potent inhibitor of this series, Cbz-L-Ala-L-Ala-AzaAsn-chloromethylketone,

displays a k(obs)/I value of 139,000 M(-1) s(-1). Other cysteine peptidases, such as papain and cathepsin B, are not inhibited by this compound at concentrations up to 100 microM. The synthetic inhibitors described here represent useful tools for the investigation of the structural and physiological properties of this unique asparagine-specific peptidase.

L7 ANSWER 14 OF 17 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:306710 SCISEARCH
THE GENUINE ARTICLE: 416ZV
TITLE: Human cystatin C, an amyloidogenic protein, dimerizes through three-dimensional domain swapping
AUTHOR: Jaskolski M (Reprint)
CORPORATE SOURCE: Adam Mickiewicz Univ, Fac Chem, Dept Crystallog, Grunwaldzka 6, PL-60780 Poznan, Poland (Reprint)
AUTHOR: Janowski R; Kozak M; Jankowska E; Grzonka Z; Grubb A; Abrahamson M
CORPORATE SOURCE: Adam Mickiewicz Univ, Fac Chem, Dept Crystallog, PL-60780 Poznan, Poland; Univ Gdansk, Dept Organ Chem, PL-80952 Gdansk, Poland; Univ Lund, Dept Clin Chem, S-22100 Lund, Sweden; Polish Acad Sci, Inst Bioorgan Chem, Ctr Biocrystallog Res, PL-61704 Poznan, Poland
COUNTRY OF AUTHOR: Poland; Sweden
SOURCE: NATURE STRUCTURAL BIOLOGY, (APR 2001) Vol. 8, No. 4, pp. 316-320.
ISSN: 1072-8368.
PUBLISHER: NATURE AMERICA INC, 345 PARK AVE SOUTH, NEW YORK, NY 10010-1707 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 30
ENTRY DATE: Entered STN: 20 Apr 2001
Last Updated on STN: 20 Apr 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The crystal structure of human cystatin C, a protein with amyloidogenic properties and a potent inhibitor of cysteine proteases, reveals how the protein refolds to produce very tight two-fold symmetric dimers while retaining the secondary structure of the monomeric form. The dimerization occurs through three-dimensional domain swapping, a mechanism for forming oligomeric proteins. The reconstituted monomer-like domains are similar to chicken cystatin except for one inhibitory loop that unfolds to form the 'open interface' of the dimer. The structure explains the tendency of human cystatin C to dimerize and suggests a mechanism for its aggregation in the brain arteries of elderly people with amyloid angiopathy, A more severe 'conformational disease' is associated with the L68Q mutant of human cystatin C, which causes massive amyloidosis, cerebral hemorrhage and death in young adults. The structure of the three-dimensional domain-swapped dimers shows how the L68Q mutation destabilizes the monomers and makes the partially unfolded intermediate less unstable. Higher aggregates may arise through the three-dimensional domain-swapping mechanism occurring in an open-ended fashion in which partially unfolded molecules are linked into infinite chains.

L7 ANSWER 15 OF 17 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1999315863 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10383426
TITLE: Inhibition of mammalian legumain by some cystatins is due to a novel second reactive site.
AUTHOR: Alvarez-Fernandez M; Barrett A J; Gerhartz B; Dando P M; Ni

J; Abrahamson M
CORPORATE SOURCE: Department of Clinical Chemistry, Institute of Laboratory Medicine, Lund University Hospital, S-221 85 Lund, Sweden.
SOURCE: The Journal of biological chemistry, (1999 Jul 2) Vol. 274, No. 27, pp. 19195-203.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 6 Aug 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 27 Jul 1999

AB We have investigated the inhibition of the recently identified family C13 cysteine peptidase, pig legumain, by human cystatin C. The cystatin was seen to inhibit enzyme activity by stoichiometric 1:1 binding in competition with substrate. The Ki value for the interaction was 0.20 nM, i.e. cystatin C had an affinity for legumain similar to that for the papain-like family C1 cysteine peptidase, cathepsin B. However, cystatin C variants with alterations in the N-terminal region and the "second hairpin loop" that rendered the cystatin inactive against cathepsin B, still inhibited legumain with Ki values 0.2-0.3 nM. Complexes between cystatin C and papain inhibited legumain activity against benzoyl-Asn-NHPhNO2 as efficiently as did cystatin C alone. Conversely, cystatin C inhibited papain activity against benzoyl-Arg-NHPhNO2 whether or not the cystatin had been incubated with legumain, strongly indicating that the cystatin inhibited the two enzymes with non-overlapping sites. A ternary complex between legumain, cystatin C, and papain was demonstrated by gel filtration supported by immunoblotting. Screening of a panel of cystatin superfamily members showed that type 1 inhibitors (cystatins A and B) and low Mr kininogen (type 3) did not inhibit pig legumain. Of human type 2 cystatins, cystatin D was non-inhibitory, whereas cystatin E/M and cystatin F displayed strong (Ki 0.0016 nM) and relatively weak (Ki 10 nM) affinity for legumain, respectively. Sequence alignments and molecular modeling led to the suggestion that a loop located on the opposite side to the papain-binding surface, between the alpha-helix and the first strand of the main beta-pleated sheet of the cystatin structure, could be involved in legumain binding. This was corroborated by analysis of a cystatin C variant with substitution of the Asn39 residue in this loop (N39K-cystatin C); this variant showed a slight reduction in affinity for cathepsin B (Ki 1.5 nM) but >>5,000-fold lower affinity for legumain (Ki >>1,000 nM) than wild-type cystatin C.

L7 ANSWER 16 OF 17 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:713452 SCISEARCH
THE GENUINE ARTICLE: 238MA
TITLE: Colorimetric and fluorimetric microplate assays for legumain and a staining reaction for detection of the enzyme after electrophoresis
AUTHOR: Barrett A J (Reprint)
CORPORATE SOURCE: Babraham Inst, Mol Enzymol Lab, MRC, Babraham CB2 4AT, Cambs, England (Reprint)
AUTHOR: Johansen H T; Knight C G
CORPORATE SOURCE: Univ Cambridge, Dept Biochem, Cambridge CB2 1QW, England; Univ Oslo, Sch Pharm, N-0316 Oslo, Norway

COUNTRY OF AUTHOR: England; Norway
SOURCE: ANALYTICAL BIOCHEMISTRY, (10 SEP 1999) Vol. 273, No. 2, pp. 278-283.
ISSN: 0003-2697.
PUBLISHER: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 19
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The cysteine endopeptidase legumain was recently discovered in mammalian cells, predominantly localized in the lysosomal system where it is believed to contribute to antigen processing for MHC class II. Here we describe rapid assay procedures for the enzyme in 96-well microplates with two substrates, a novel compound, succinyl-Ala-Ala-Asn-4-methoxy-2-naphthylamide, and benzyloxycarbonyl-Ala-Ala-Asn-4-methyl-7-coumarylamide. Both substrates are suitable for fluorimetric assays, but the naphthylamide also allows colorimetric detection of legumain activity, since the released 4-methoxy-2-naphthylamine gives a red product when coupled with the Fast Garnet color reagent. We show that the naphthylamide substrate can be used to visualize active legumain after electrophoresis in polyacrylamide gel. Both substrates provide assays that are reproducible and sufficiently sensitive to allow the assay of legumain in crude samples such as tissue homogenates, although the coumarylamide is the more sensitive. The specificity of both assay methods for legumain was verified by the lack of inhibition by E-64 and total inhibition by eggwhite cystatin. (C) 1999 Academic Press.

L7 ANSWER 17 OF 17 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 1997218252 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9065484
TITLE: Cloning, isolation, and characterization of mammalian legumain, an asparaginyl endopeptidase.
AUTHOR: Chen J M; Dando P M; Rawlings N D; Brown M A; Young N E; Stevens R A; Hewitt E; Watts C; Barrett A J
CORPORATE SOURCE: Medical Research Council Peptidase Laboratory, Department of Immunology, The Babraham Institute, Babraham Hall, Babraham, Cambridgeshire CB2 4AT, United Kingdom.
SOURCE: The Journal of biological chemistry, (1997 Mar 21) Vol. 272, No. 12, pp. 8090-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-Y09862
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 6 May 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 18 Apr 1997

AB Legumain is a cysteine endopeptidase that shows strict specificity for hydrolysis of asparaginyl bonds. The enzyme belongs to peptidase family C13, and is thus unrelated to the better known cysteine peptidases of the papain family, C1 (Rawlings, N. D., and Barrett, A. J. (1994) Methods Enzymol. 244, 461-486). To date, legumain has been described only from plants and a blood fluke, Schistosoma mansoni. We now show that legumain is present in mammals. We have cloned and sequenced human legumain and part of pig legumain.

We have also purified legumain to homogeneity (2200-fold, 8% yield) from pig kidney. The mammalian sequences are clearly homologous with legumains from non-mammalian species. Pig legumain is a glycoprotein of about 34 kDa, decreasing to 31 kDa on deglycosylation. It is an asparaginyl endopeptidase, hydrolyzing Z-Ala-Ala-Asn-7-(4-methyl)coumarylamide and benzoyl-Asn-p-nitroanilide. Maximal activity is seen at pH 5.8 under normal assay conditions, and the enzyme is irreversibly denatured at pH 7 and above. Mammalian legumain is a cysteine endopeptidase, inhibited by iodoacetamide and maleimides, but unaffected by compound E64 (trans-epoxysuccinyl-L-leucylamido-(4-guanidino)butane). It is inhibited by ovocystatin (cystatin from chicken egg white) and human cystatin C with Ki values < 5 nM. We discuss the significance of the discovery of a cysteine endopeptidase of a new family and distinctive specificity in man and other mammals.

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                enhanced
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                  pre-registered REACH substances
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                  coverage of complete UK patent families
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=> s cystatin
L1        9175 CYSTATIN

=> s cathepsin s
L2        1382 CATHEPSIN S

=> s l1 and l2
L3         195 L1 AND L2

=> dup rem l3
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PROCESSING COMPLETED FOR L3
L4          116 DUP REM L3 (79 DUPLICATES REMOVED)

=> s cystatin c
L5         5814 CYSTATIN C

=> s l5 and l4
L6           78 L5 AND L4

=> d ibib abs 1-78

L6   ANSWER 1 OF 78     MEDLINE on STN
ACCESSION NUMBER:   2008541080     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 18635848
TITLE:              Cathepsin B, K, and S are expressed in cerebral aneurysms
                    and promote the progression of cerebral aneurysms.
AUTHOR:             Aoki Tomohiro; Kataoka Hiroharu; Ishibashi Ryota; Nozaki
                    Kazuhiko; Hashimoto Nobuo
CORPORATE SOURCE:   Department of Neurosurgery, Kyoto University Graduate
                    School of Medicine, 54 Kawaharacho, Shogoin, Sakyo-ku,
                    Kyoto, 606-8507, Japan.. kataoka@kuhp.kyoto-u.ac.jp
SOURCE:             Stroke; a journal of cerebral circulation, (2008 Sep) Vol.
                    39, No. 9, pp. 2603-10.  Electronic Publication:
                    2008-07-17.
                    Journal code: 0235266. E-ISSN: 1524-4628.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
                    (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200809
ENTRY DATE:         Entered STN: 27 Aug 2008
                    Last Updated on STN: 26 Sep 2008
                    Entered Medline: 25 Sep 2008
AB   BACKGROUND AND PURPOSE: A cerebral aneurysm (CA) causes catastrophic
     subarachnoid hemorrhage.  Degradation of extracellular matrix in arterial
     walls is a prominent feature of cerebral aneurysms.  We investigated the
     expression and role of cysteine cathepsins, collagen- and elastin-
     degrading proteinases, in CA progression.  METHODS: CAs were induced in
     Sprague-Dawley rats with or without cysteine cathepsin inhibitor, NC-2300.
     Expression of cathepsin B, K, S, and cystatin C, an
     endogenous inhibitor of cysteine cathepsins, in aneurysmal walls was
     examined in quantitative RT-PCR and immunohistochemistry.  The activity of
     cysteine cathepsins and collagenase I and IV in aneurysmal walls was also
     assessed.  Finally, expression of cysteine cathepsins and cystatin
     C in human CAs was examined.  RESULTS: Quantitative RT-PCR and
     immunohistochemistry revealed upregulated expression of cathepsin B, K,
     and S in the late stage of aneurysm progression.  In contrast,
     cystatin C expression was reduced with aneurysm
     progression.  Treatment with NC-2300 resulted in the decreased incidence
     of advanced CAs.  The activity of cysteine cathepsins and collagenase I
     and IV in aneurysmal walls was reduced and elastin content was increased
     in the NC-2300-treated group.  Finally, immunohistochemistry for cysteine
     cathepsins and cystatin C expression in human CAs
     showed the same expression pattern as in the rat study.  CONCLUSIONS: Data
     obtained by using NC-2300 revealed an important role of cysteine
     cathepsins in the progression of CAs.  Our findings strongly suggest that
     an imbalance between cysteine cathepsins and their inhibitor may cause the
     excessive breakdown of extracellular matrix in the arterial walls leading
     to the progression and rupture of CAs.

L6   ANSWER 2 OF 78     MEDLINE on STN
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ACCESSION NUMBER: 2008345018 MEDLINE
DOCUMENT NUMBER: PubMed ID: 18508621
TITLE: Cystatin C and cathepsins in cardiovascular disease.
AUTHOR: Bengtsson Eva; Nilsson Jan; Jovinge Stefan
CORPORATE SOURCE: Department of Clinical Sciences, Experimental Cardiovascular Research Unit, Lund University, Malmo, Sweden.. eva.bengtsson@med.lu.se
SOURCE: Frontiers in bioscience : a journal and virtual library, (2008) Vol. 13, pp. 5780-6. Electronic Publication: 2008-05-01. Ref: 62
Journal code: 9709506. E-ISSN: 1093-4715.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200809
ENTRY DATE: Entered STN: 30 May 2008
Last Updated on STN: 20 Sep 2008
Entered Medline: 19 Sep 2008

AB Cystatin C and cathepsins could play a role in almost all processes involved in atherosclerotic lesion formation by their degradation of extracellular matrix proteins and apolipoprotein B100, the protein moiety of LDL. Several cysteine cathepsins are upregulated in human lesions accompanied by a decrease in cystatin C, the major inhibitor of cysteine cathepsins. Recent research show that atherosclerotic mice deficient in cystatin C display increased elastic lamina degradation as well as larger plaque formation. Cathepsin S- and K-deficient atherosclerotic mice, on the other hand, both have less atherosclerosis, where cathepsin S-/- mice exhibited fewer plaque ruptures and cathepsin K-/- larger foam cells than control mice. This article reviews possible roles of cystatin C and cathepsins in different processes and stages of the atherosclerotic disease.

L6 ANSWER 3 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2007410928 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17539023
TITLE: Impairment of microglial responses to facial nerve axotomy in cathepsin S-deficient mice.
AUTHOR: Hao Hai Peng; Doh-Ura Katsumi; Nakanishi Hiroshi
CORPORATE SOURCE: Laboratory of Oral Aging Science, Faculty of Dental Sciences, Kyushu University, Fukuoka, Japan.
SOURCE: Journal of neuroscience research, (2007 Aug 1) Vol. 85, No. 10, pp. 2196-206.
Journal code: 7600111. ISSN: 0360-4012.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200711
ENTRY DATE: Entered STN: 17 Jul 2007
Last Updated on STN: 2 Nov 2007
Entered Medline: 1 Nov 2007

AB Cathepsin S (CS) is a lysosomal/endosomal cysteine protease especially expressed in cells of a mononuclear lineage including microglia. To better understand the role of CS in microglia, we investigated microglial responses after a facial nerve axotomy in CS-deficient (CS-/-) and wild-type mice. Microglia in both groups

accumulated in the facial motor nucleus following axotomy. However, the mean number of microglia in CS-/- mice on the axotomized side was significantly smaller than that in wild-type mice. Microglia were found to adhere to injured motoneurons in wild-type mice, whereas microglia abutted on injured motoneurons without spreading on their surface in CS-/- mice. At the same time, the axotomy-induced down-regulation of tenasin-R, an antiadhesive perineuronal net for microglia, was partially abrogated in CS-/- mice. Primary cultured microglia prepared from CS-/- mice showed that CS deficiency caused significant suppression of migration and transmigration of microglia. In CS-/- mice, impaired recruitments of circulating monocytes and T lymphocytes and reduced expression of the class II major compatibility complex on the axotomized side were observed. Interestingly, cathepsin B, a typical lysosomal cysteine protease, was markedly expressed on the axotomized side in CS-/- but not in wild-type microglia. Finally, we compared axotomy-induced neuronal death in the two groups and found that the percentage of motoneurons that survived in CS-/- mice was significantly smaller than that in wild-type mice. The present study strongly suggests that CS plays a role in the migration and activation of microglia to protect facial motoneurons against axotomy-induced injury.

L6 ANSWER 4 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2007122286 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17322367
TITLE: Collagen degradation in the abdominal aneurysm: a conspiracy of matrix metalloproteinase and cysteine collagenases.
AUTHOR: Abdul-Hussien Hazem; Soekhoe Ratna G V; Weber Ekkehard; von der Thusen Jan H; Kleemann Robert; Mulder Adri; van Bockel J Hajo; Hanemaaijer Roeland; Lindeman Jan H N
CORPORATE SOURCE: Department of Vascular Surgery, Leiden University Medical Center, Leiden, The Netherlands.
SOURCE: The American journal of pathology, (2007 Mar) Vol. 170, No. 3, pp. 809-17.
Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200705
ENTRY DATE: Entered STN: 27 Feb 2007
Last Updated on STN: 2 May 2007
Entered Medline: 1 May 2007

AB Growth and rupture of abdominal aortic aneurysms (AAAs) result from increased collagen turnover. Collagen turnover critically depends on specific collagenases that cleave the triple helical region of fibrillar collagen. As yet, the collagenases responsible for collagen degradation in AAAs have not been identified. Increased type I collagen degradation products confirmed collagen turnover in AAAs (median values: <1, 43, and 108 ng/mg protein in control, growing, and ruptured AAAs, respectively). mRNA and protein analysis identified neutrophil collagenase [matrix metalloproteinase (MMP)-8] and cysteine collagenases cathepsin K, L, and S as the principle collagenases in growing and ruptured AAAs. Except for modestly increased MMP-14 mRNA levels, collagenase expression was similar in growing and ruptured AAAs (anterior-lateral wall). Evaluation of posttranslational regulation of protease activity showed a threefold increase in MMP-8, a fivefold increase in cathepsins K and L, and a 30-fold increase in cathepsin S activation in growing and ruptured AAAs. The presence of the osteoclastic proton pump indicated optimal conditions for extracellular cysteine protease activity. Protease

inhibitor mRNA expression was similar in AAAs and controls, but AAA protein levels of cystatin C, the principle cysteine protease inhibitor, were profoundly reduced (>80%). We found indications that this secondary deficiency relates to cystatin C degradation by (neutrophil-derived) proteases.

L6 ANSWER 5 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2006553664 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16825321
TITLE: Cathepsin s promotes human preadipocyte differentiation: possible involvement of fibronectin degradation.
AUTHOR: Taleb Soraya; Cancello Raffaella; Clement Karine; Lacasa Daniele
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale, Unite 755, Department of Nutrition, Hotel-Dieu, Place du parvis Notre-Dame, 75004 Paris, France.
SOURCE: Endocrinology, (2006 Oct) Vol. 147, No. 10, pp. 4950-9. Electronic Publication: 2006-07-06. Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200610
ENTRY DATE: Entered STN: 19 Sep 2006 Last Updated on STN: 24 Oct 2006 Entered Medline: 24 Oct 2006
AB We previously showed that the cysteine protease cathepsin S (CTSS), known to degrade several components of the extracellular matrix (ECM), is produced by human adipose cells and increased in obesity. Because ECM remodeling is a key process associated with adipogenesis, this prompted us to assess the potential role of CTSS to promote preadipocyte differentiation. Kinetic studies in primary human preadipocytes revealed a modest increase in CTSS gene expression and secretion at the end of differentiation. CTSS activity was maximal in preadipocyte culture medium but decreased thereafter, fitting with increased release of the CTSS endogenous inhibitor, cystatin C, during differentiation. Inhibition of CTSS activity by an exogenous-specific inhibitor added along the differentiation, resulted in a 2-fold reduction of lipid content and expression of adipocyte markers in differentiated cells. Conversely, the treatment of preadipocytes with human recombinant CTSS increased adipogenesis. Moreover, CTSS supplementation in preadipocyte media markedly reduced the fibronectin network, a key preadipocyte-ECM component, the decrease of which is required for adipogenesis. Using immunohistochemistry on serial sections of adipose tissue of obese subjects, we showed that adipose cells staining positive for CTSS are mainly located in the vicinity of fibrosis regions containing fibronectin. Herein we propose that CTSS may promote human adipogenesis, at least in part, by degrading fibronectin in the early steps of differentiation. Taken together, these results indicate that CTSS released locally by preadipocytes promotes adipogenesis, suggesting a possible contribution of this protease to fat mass expansion in obesity.

L6 ANSWER 6 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2006433806 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16728655
TITLE: Increased expression of elastolytic cathepsins S, K, and V and their inhibitor cystatin C in stenotic aortic valves.
AUTHOR: Helske Satu; Syvaranta Suvi; Lindstedt Ken A; Lappalainen

Jani; Oorni Katariina; Mayranpaa Mikko I; Lommi Jyri; Turto Heikki; Werkkala Kalervo; Kupari Markku; Kovanen Petri T
CORPORATE SOURCE: Wihuri Research Institute, Kalliolinnantie 4, FIN-00140 Helsinki, Finland.
SOURCE: Arteriosclerosis, thrombosis, and vascular biology, (2006 Aug) Vol. 26, No. 8, pp. 1791-8. Electronic Publication: 2006-05-25.
Journal code: 9505803. E-ISSN: 1524-4636.
PUB. COUNTRY: United States
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200608
ENTRY DATE: Entered STN: 22 Jul 2006
Last Updated on STN: 10 Aug 2006
Entered Medline: 9 Aug 2006

AB OBJECTIVE: To investigate the possible role of elastolytic cathepsins S, K, and V and their endogenous inhibitor cystatin C in adverse extracellular matrix remodeling of stenotic aortic valves. METHODS AND RESULTS: Stenotic aortic valves were collected at valve replacement surgery and control valves at cardiac transplantations. The expression of cathepsins S, K, and V and cystatin C was studied by conventional and real-time polymerase chain reaction and by immunohistochemistry. Total cathepsin activity in the aortic valves was quantified by a fluorometric microassay. When compared with control valves, stenotic valves showed increased mRNA expression of cathepsins S, K, and V ($P<0.05$ for each) and a higher total cathepsin activity ($P<0.001$). In stenotic valves, cystatin C mRNA was increased ($P<0.05$), and cystatin C protein was found particularly in areas with infiltrates of inflammatory cells. Both cathepsin S and cystatin C were present in bony areas of the valves, whereas cathepsin V localized to endothelial cells in areas rich of neovascularization. Incubation of thin sections of aortic valves with cathepsins S, K, and V resulted in severe disruption of elastin fibers, and this cathepsin effect could be blocked by adding cystatin C to the incubation system. CONCLUSIONS: Stenotic aortic valves show increased expression and activity of elastolytic cathepsins S, K, and V. These cathepsins may accelerate the destruction of aortic valvular extracellular matrix, so promoting the progression of aortic stenosis.

L6 ANSWER 7 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2006271733 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16140306
TITLE: Increased serum cathepsin S in patients with atherosclerosis and diabetes.
AUTHOR: Liu Jian; Ma Likun; Yang Jintian; Ren An; Sun Zimin; Yan Gengxing; Sun Jiusong; Fu Huanxian; Xu Weihua; Hu Chengcheng; Shi Guo-Ping
CORPORATE SOURCE: Department of Molecular and Cell Biology, School of Life Sciences, University of Science and Technology of China, Hefei, China.
CONTRACT NUMBER: HL-60942 (United States NHLBI)
HL-67283 (United States NHLBI)
SOURCE: Atherosclerosis, (2006 Jun) Vol. 186, No. 2, pp. 411-9. Electronic Publication: 2005-09-02.
Journal code: 0242543. ISSN: 0021-9150.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)

(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200611
ENTRY DATE: Entered STN: 17 May 2006
Last Updated on STN: 2 Nov 2006
Entered Medline: 1 Nov 2006

AB Atherosclerosis and diabetes are closely associated and both involve extensive degradation of the aortic elastin. Increased elastase activity has been detected in diabetic animal aortae. We have demonstrated enhanced elastolytic cathepsin S in human atherosclerotic lesions but insufficient amounts of its endogenous inhibitor cystatin C, suggesting alterations of serum cathepsin S and/or cystatin C in patients with atherosclerosis or diabetes. In this study, we measured levels of both cathepsin S and cystatin C in sera from 240 patients by ELISA. Among these patients, 107 had a diagnosis of atherosclerotic stenosis, 103 were diabetic, and 30 had neither condition. Multiple linear regression analysis demonstrated that significantly higher serum levels of cathepsin S in patients with either atherosclerotic stenosis ($p<0.04$) or diabetes ($p=0.0005$) persisted after adjustment for cystatin C level, renal function, smoking, and serum glucose levels ($p=0.008$, $p=0.0005$). Furthermore, patients with acute ($p=0.009$) or previous myocardial infarction ($p<0.02$) or unstable angina pectoris ($p<0.05$) had elevated levels of cathepsin S after adjustment for smoking, creatinine, cystatin C, and serum glucose. In contrast, serum cystatin C levels were higher in diabetic patients ($p=0.00001$), but not in atherosclerotic subjects ($p=0.14$), than in the non-involved population after adjustment for age, smoking, and renal function. Although the pathophysiology of cathepsin S or cystatin C in atherosclerosis and diabetes requires further investigation, increased serum cathepsin S may serve as a biomarker for both diseases.

L6 ANSWER 8 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2006114144 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16365041
TITLE: Cathepsin S controls angiogenesis and tumor growth via matrix-derived angiogenic factors.
AUTHOR: Wang Bing; Sun Jiusong; Kitamoto Shiro; Yang Min; Grubb Anders; Chapman Harold A; Kalluri Raghu; Shi Guo-Ping
CORPORATE SOURCE: Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 77 Ave. Louis Pasteur, Boston, MA 02115, USA.
CONTRACT NUMBER: DK 62987 (United States NIDDK)
HL 48621 (United States NHLBI)
HL 60942 (United States NHLBI)
HL 67283 (United States NHLBI)
SOURCE: The Journal of biological chemistry, (2006 Mar 3) Vol. 281, No. 9, pp. 6020-9. Electronic Publication: 2005-12-19. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200605
ENTRY DATE: Entered STN: 28 Feb 2006
Last Updated on STN: 24 May 2006
Entered Medline: 23 May 2006

AB The cysteine protease cathepsin S is highly expressed in malignant tissues. By using a mouse model of multistage murine pancreatic islet cell carcinogenesis in which cysteine cathepsin activity has been functionally implicated, we demonstrated that selective cathepsin S deficiency impaired angiogenesis and tumor cell proliferation, thereby impairing angiogenic islet formation and the growth of solid tumors, whereas the absence of its endogenous inhibitor cystatin C resulted in opposite phenotypes. Although mitogenic vascular endothelial growth factor, transforming growth factor-beta1, and the anti-angiogenic endostatin levels in either serum or carcinoma tissue extracts did not change in cathepsin S - or cystatin C-null mice, tumor tissue basic fibroblast growth factor and serum type 1 insulin growth factor levels were higher in cystatin C-null mice, and serum type 1 insulin growth factor levels were also increased in cathepsin S-null mice. Furthermore, cathepsin S affected the production of type IV collagen-derived anti-angiogenic peptides and the generation of bioactive pro-angiogenic gamma2 fragments from laminin-5, revealing a functional role for cathepsin S in angiogenesis and neoplastic progression.

L6 ANSWER 9 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2006050025 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16436681
TITLE: Localization of cysteine protease, cathepsin S, to the surface of vascular smooth muscle cells by association with integrin alphanubeta3.
AUTHOR: Cheng Xian Wu; Kuzuya Masafumi; Nakamura Kae; Di Qun; Liu Zexuan; Sasaki Takeshi; Kanda Shigeru; Jin Hai; Shi Guo-Ping; Murohara Toyoaki; Yokota Mitsuhiro; Iguchi Akihisa
CORPORATE SOURCE: Department of Geriatrics, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan.
SOURCE: The American journal of pathology, (2006 Feb) Vol. 168, No. 2, pp. 685-94.
Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 27 Jan 2006
Last Updated on STN: 22 Mar 2006
Entered Medline: 21 Mar 2006

AB Smooth muscle cell (SMC) migration from the tunica media to the intima, a key event in neointimal formation, requires proteolytic degradation of elastin-rich extracellular matrix barriers. Although cathepsin S (Cat S) is overexpressed in atherosclerotic and neointimal lesions, its exact role in SMC behavior remains primarily unresolved. We examined the involvement of Cat S on SMC migration through an extracellular matrix barrier and its localization in SMCs. A selective Cat S inhibitor and the endogenous inhibitor cystatin C significantly attenuated SMC invasion across elastin gel. Western blotting and cell surface biotinylation analysis demonstrated localization of the 28-kd active form of Cat S on the SMC surface, consistent with its role in the proteolysis of subcellular matrices. Treatment with interferon-gamma or interleukin-beta1 significantly augmented the ability of SMC membranes to degrade elastin along with a significant increase in the level of active Cat S compared with controls. Immunofluorescence and confocal microscopy showed a punctuated pattern of Cat S clusters at the periphery of SMCs; further studies demonstrated partial co-localization of

Cat S and integrin alphanubeta3 at the cell surfaces. These findings demonstrate that active Cat S co-localizes with integrin alphanubeta3 as a receptor on the SMC surface, playing an important role in the invasive behavior of SMCs.

L6 ANSWER 10 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2005647890 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16286017
TITLE: IL-6-STAT3 controls intracellular MHC class II alphabeta dimer level through cathepsin S activity in dendritic cells.
AUTHOR: Kitamura Hidemitsu; Kamon Hokuto; Sawa Shin-Ichiro; Park Sung-Joo; Katunuma Nobuhiko; Ishihara Katsuhiko; Murakami Masaaki; Hirano Toshio
CORPORATE SOURCE: Laboratory for Cytokine Signaling, RIKEN Research Center for Allergy and Immunology, Yokohama 230-0045, Japan.
SOURCE: Immunity, (2005 Nov) Vol. 23, No. 5, pp. 491-502. Journal code: 9432918. ISSN: 1074-7613.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200512
ENTRY DATE: Entered STN: 8 Dec 2005
Last Updated on STN: 31 Dec 2005
Entered Medline: 30 Dec 2005
AB We found IL-6-STAT3 pathway suppresses MHC class II (MHCII) expression on dendritic cells (DCs) and attenuates T cell activation. Here, we showed that IL-6-STAT3 signaling reduced intracellular MHCII alphabeta dimmer, Ii, and H2-DM levels in DCs. IL-6-mediated STAT3 activation decreased cystatin C level, an endogenous inhibitor of cathepsins, and enhanced cathepsin activities. Importantly, cathepsin S inhibitors blocked reduction of MHCII alphabeta dimer, Ii, and H2-DM in the IL-6-treated DCs. Overexpression of cystatin C suppressed IL-6-STAT3-mediated increase of cathepsin S activity and reduction of MHCII alphabeta dimer, Ii, and H2-DM levels in DCs. Cathepsin S overexpression in DCs decreased intracellular MHCII alphabeta dimer, Ii, and H2-DM levels, LPS-mediated surface expression of MHCII and suppressed CD4(+) T cell activation. IL-6-gp130-STAT3 signaling in vivo decreased cystatin C expression and MHCII alphabeta dimer level in DCs. Thus, IL-6-STAT3-mediated increase of cathepsin S activity reduces the MHCII alphabeta dimer, Ii, and H2-DM levels in DCs, and suppresses CD4(+) T cell-mediated immune responses.

L6 ANSWER 11 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2005237480 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15872057
TITLE: Presence of anti-cystatin C-positive dendritic cells or macrophages and localization of cysteine proteases in the apical bud of the enamel organ in the rat incisor.
AUTHOR: Nishikawa Sumio
CORPORATE SOURCE: Department of Biology, Tsurumi University School of Dental Medicine, 2-1-3 Tsurumi, Tsurumi-ku, Yokohama 230-8501, Japan.. nishikawa-s@tsurumi-u.ac.jp
SOURCE: The journal of histochemistry and cytochemistry : official journal of the Histochemistry Society, (2005 May) Vol. 53, No. 5, pp. 643-51. Journal code: 9815334. ISSN: 0022-1554.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 6 May 2005
Last Updated on STN: 17 Jun 2005
Entered Medline: 16 Jun 2005

AB Cystatin C, a cysteine protease inhibitor, was examined in the apical buds of rat incisors by immunohistochemistry, because in transition and maturation zones most of the dendritic cells in the papillary layer are anti-cystatin C-positive. Anti-cystatin C-labeled cells were sparse and localized to the proliferation and differentiation zones, constituting the apical bud of 5-week-old rat incisors. These cells were considered macrophages or dendritic cells, based on their reactivity with OX6 and ED1, as well as their ultrastructure. Basement membrane at the periphery of apical bud was also labeled by anti-cystatin C antibody. The apical buds included a few apoptotic fragments and weak reactivity with antibody to cathepsin L, a cysteine protease. Reactivity to anti-cystatin C and anti-cathepsin L antibodies was also detected in the apical bud of newborn rat incisors. These results suggest that the cystatin C-positive macrophages or dendritic cells are involved in normal incisor formation. They may be related to the clearance of apoptotic cells or protection from putative cysteine protease activity.

L6 ANSWER 12 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2004392733 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15178558
TITLE: Lysosomal cysteine proteases in atherosclerosis.
AUTHOR: Liu Jian; Sukhova Galina K; Sun Jiu-Song; Xu Wei-Hua; Libby Peter; Shi Guo-Ping
CORPORATE SOURCE: Department of Molecular and Cell Biology, School of Life Science, University of Science and Technology of China, Hefei, Anhui, China.
CONTRACT NUMBER: HL 60942 (United States NHLBI)
HL 67249 (United States NHLBI)
HL-56985 (United States NHLBI)
HL67283 (United States NHLBI)
SOURCE: Arteriosclerosis, thrombosis, and vascular biology, (2004 Aug) Vol. 24, No. 8, pp. 1359-66. Electronic Publication: 2004-06-03. Ref: 83
Journal code: 9505803. E-ISSN: 1524-4636.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 7 Aug 2004
Last Updated on STN: 11 Feb 2005
Entered Medline: 10 Feb 2005

AB Atherosclerosis is an inflammatory disease characterized by extensive remodeling of the extracellular matrix architecture of the arterial wall. Although matrix metalloproteinases and serine proteases participate in these pathologic events, recent data from atherosclerotic patients and animals suggest the participation of lysosomal cysteine proteases in atherogenesis. Atherosclerotic lesions in humans overexpress the elastolytic and collagenolytic cathepsins S, K, and L but show relatively

reduced expression of cystatin C, their endogenous inhibitor, suggesting a shift in the balance between cysteine proteases and their inhibitor that favors remodeling of the vascular wall. Extracts of human atheromatous tissue show greater elastolytic activity in vitro than do those from healthy donors. The cysteinyl protease inhibitor E64d limits this increased elastolysis, indicating involvement of cysteine proteases in elastin degradation during atherogenesis. Furthermore, inflammatory cytokines augment expression and secretion of active cysteine proteases from cultured monocyte-derived macrophages, vascular smooth muscle cells, and endothelial cells and increase degradation of extracellular elastin and collagen. Cathepsin S -deficient cells or those treated with E64d show significantly impaired elastolytic or collagenolytic activity. Additionally, recent in vivo studies of atherosclerosis-prone, LDL receptor-null mice lacking cathepsin S show participation of this enzyme in the initial infiltration of leukocytes, medial elastic lamina degradation, endothelial cell invasion, and neovascularization, illustrating an important role for cysteine proteases in arterial remodeling and atherogenesis.

L6 ANSWER 13 OF 78 MEDLINE on STN

ACCESSION NUMBER: 2004259242 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15158154
TITLE: Cathepsin S expression is up-regulated following balloon angioplasty in the hypercholesterolemic rabbit.
AUTHOR: Burns-Kurtis Cynthia L; Olzinski Alan R; Needle Saul; Fox Josephine H; Capper Elizabeth A; Kelly Fiona M; McQueney Michael S; Romanic Anne M
CORPORATE SOURCE: Department of Vascular Inflammatory Diseases, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406, USA.. cynthia_l_kurtis@gsk.com
SOURCE: Cardiovascular research, (2004 Jun 1) Vol. 62, No. 3, pp. 610-20.
Journal code: 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 26 May 2004
Last Updated on STN: 5 Oct 2004
Entered Medline: 4 Oct 2004

AB OBJECTIVE: Neointimal development following balloon angioplasty involves many factors including smooth muscle cell (SMC) migration and proliferation and extracellular matrix (ECM) remodeling. Further, in hypercholesterolemic (HC) conditions, there is an influx of macrophage foam cells (FCs) into the restenotic lesion, which also involves degradation of the basement membrane and surrounding ECM. The ECM remodeling that occurs during restenosis has been shown to be mediated by various proteases. Here we have investigated the role of cathepsin S (CatS), a cysteine protease, in this process. METHODS AND RESULTS: We have demonstrated by Taqman quantitative PCR, Western blot, and immunohistochemistry that CatS is up-regulated in restenotic lesions of HC rabbits following balloon injury of the iliofemoral artery. CatS mRNA expression was elevated 28-fold in balloon-injured vessels relative to uninjured contralateral vessels in HC rabbits 8 weeks post-angioplasty ($p<0.05$). CatS protein expression was detected within 1 day post-injury, persisted throughout the entire time course evaluated (60 days post-injury), and was co-localized with SMCs, macrophages, and FCs. In contrast, cystatin C (CysC),

the endogenous inhibitor of cathepsins, was only minimally up-regulated following injury. CysC mRNA expression was elevated 3.5-fold in balloon-injured vessels relative to uninjured contralateral vessels in HC rabbits 8 weeks post-angioplasty ($p<0.005$), and up-regulation of protein expression was not detected until days 28 and 60 post-injury. Additional biochemical studies using recombinant rabbit CatS revealed that rabbit CatS digests laminin, fibronectin, and type I collagen. Further, CatS expression was evaluated in SMCs that were induced to migrate through a matrix-coated Boyden chamber upon platelet-derived growth factor (PDGF) stimulation. The addition of a selective CatS inhibitor reduced SMC migration dose-dependently with an 80% reduction in migration at 30 nM ($p<0.005$). Additionally, we have shown that CatS protein expression by human macrophages was increased upon stimulation with oxidized low density lipoprotein (ox-LDL), implying augmentation of CatS production during foam cell formation. CONCLUSION: Taken together, our results indicate an enhanced expression of CatS during neointima formation and it is associated with invading SMCs, macrophages, and FCs, highlighting the importance of CatS in the pathogenesis of restenosis.

L6 ANSWER 14 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2003612205 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14695337
TITLE: Increased expression of elastolytic cysteine proteases, cathepsins S and K, in the neointima of balloon-injured rat carotid arteries.
AUTHOR: Cheng Xian Wu; Kuzuya Masafumi; Sasaki Takeshi; Arakawa Koji; Kanda Shigeru; Sumi Daigo; Koike Teruhiko; Maeda Keiko; Tamaya-Mori Norika; Shi Guo-Ping; Saito Noboru; Iguchi Akihisa
CORPORATE SOURCE: Department of Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan.
SOURCE: The American journal of pathology, (2004 Jan) Vol. 164, No. 1, pp. 243-51.
Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 30 Dec 2003
Last Updated on STN: 2 Mar 2004
Entered Medline: 27 Feb 2004

AB The matrix-degrading activity of several proteases are involved in the accelerated breakdown of extracellular matrix associated with vascular remodeling during the development of atherosclerosis and vascular injury-induced neointimal formation. Previous studies have shown that the potent elastolytic cysteine proteases, cathepsins S and K, are overexpressed in atherosclerotic lesions in human and animal models. However, the role of these cathepsins in vascular remodeling remains unclear. In the present study, the expressions of cathepsin S and K and their inhibitor cystatin C were examined during arterial remodeling using a rat carotid artery balloon-injury model. The increase in both cathepsin S and K mRNA levels was observed from day 1 and day 3 through day 14 following the induction of balloon injury, respectively. Western blotting analysis revealed that both cathepsin S and K protein levels also increased in the carotid arteries during neointima formation, coinciding with an increase elastolytic activity assayed using Elastin-Congo red, whereas, no significant change in the expressions of cystatin C mRNA and protein was observed during follow-up periods after injury. Immunohistochemistry, Western blot, and in situ hybridization showed that the increase of cathepins S and K and

the decrease of cystatin C occurred preferentially in the developing neointima. These findings suggest that cathepsin S and K may participate in the pathological arterial remodeling associated with restenosis.

L6 ANSWER 15 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2003530180 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14607896
TITLE: The protease inhibitor cystatin C is differentially expressed among dendritic cell populations, but does not control antigen presentation.
AUTHOR: El-Sukkari Dima; Wilson Nicholas S; Hakansson Katarina; Steptoe Raymond J; Grubb Anders; Shortman Ken; Villadangos Jose A
CORPORATE SOURCE: The Walter and Eliza Hall Institute of Medical Research, Victoria, Melbourne, Australia.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2003 Nov 15) Vol. 171, No. 10, pp. 5003-11. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 11 Nov 2003
Last Updated on STN: 19 Feb 2004
Entered Medline: 18 Feb 2004

AB Dendritic cells (DC) undergo complex developmental changes during maturation. The MHC class II (MHC II) molecules of immature DC accumulate in intracellular compartments, but are expressed at high levels on the plasma membrane upon DC maturation. It has been proposed that the cysteine protease inhibitor cystatin C (CyC) plays a pivotal role in the control of this process by regulating the activity of cathepsin S, a protease involved in removal of the MHC II chaperone Ii, and hence in the formation of MHC II-peptide complexes. We show that CyC is differentially expressed by mouse DC populations. CD8(+) DC, but not CD4(+) or CD4(-)CD8(-) DC, synthesize CyC, which accumulates in MHC II(+)Lamp(+) compartments. However, Ii processing and MHC II peptide loading proceeded similarly in all three DC populations. We then analyzed MHC II localization and Ag presentation in CD8(+) DC, bone marrow-derived DC, and spleen-derived DC lines, from CyC-deficient mice. The absence of CyC did not affect the expression, the subcellular distribution, or the formation of peptide-loaded MHC II complexes in any of these DC types, nor the efficiency of presentation of exogenous Ags. Therefore, CyC is neither necessary nor sufficient to control MHC II expression and Ag presentation in DC. Our results also show that CyC expression can differ markedly between closely related cell types, suggesting the existence of hitherto unrecognized mechanisms of control of CyC expression.

L6 ANSWER 16 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2003133142 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12639996
TITLE: Deficiency of cathepsin S reduces atherosclerosis in LDL receptor-deficient mice.
AUTHOR: Sukhova Galina K; Zhang Yaou; Pan Jie-Hong; Wada Youichiro; Yamamoto Takashi; Naito Makoto; Kodama Tatsuhiko; Tsimikas Sotirios; Witztum Joseph L; Lu Michael L; Sakara Yasuhiko; Chin Michael T; Libby Peter; Shi Guo-Ping
CORPORATE SOURCE: The Leducq Center for Cardiovascular Research, Department of Medicine, Brigham and Women's Hospital and Harvard

Medical School, Boston, Massachusetts, USA.
CONTRACT NUMBER: HL-34636 (United States NHLBI)
HL-56985 (United States NHLBI)
HL-60942 (United States NHLBI)
SOURCE: The Journal of clinical investigation, (2003 Mar) Vol. 111, No. 6, pp. 897-906.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 22 Mar 2003
Last Updated on STN: 3 Apr 2003
Entered Medline: 2 Apr 2003

AB Human atherosclerotic lesions overexpress the lysosomal cysteine protease cathepsin S (Cat S), one of the most potent mammalian elastases known. In contrast, atheromata have low levels of the endogenous Cat S inhibitor cystatin C compared with normal arteries, suggesting involvement of this protease in atherogenesis. The present study tested this hypothesis directly by crossing Cat S-deficient (CatS(-/-)) mice with LDL receptor-deficient (LDLR(-/-)) mice that develop atherosclerosis on a high-cholesterol diet. Compared with LDLR(-/-) mice, double-knockout mice (CatS(-/-)LDLR(-/-)) developed significantly less atherosclerosis, as indicated by plaque size (plaque area and intimal thickening) and stage of development. These mice also had markedly reduced content of intimal macrophages, lipids, smooth muscle cells, collagen, CD4(+) T lymphocytes, and levels of IFN-gamma. CatS(-/-)LDLR(-/-) monocytes showed impaired subendothelial basement membrane transmigration, and aortas from CatS(-/-)LDLR(-/-) mice had preserved elastic laminae. These findings establish a pivotal role for Cat S in atherogenesis.

L6 ANSWER 17 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2002454842 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12213722
TITLE: Differential expression of cysteine and aspartic proteases during progression of atherosclerosis in apolipoprotein E-deficient mice.
AUTHOR: Jormsjo Sofia; Wuttge Dirk M; Sirsjo Allan; Whatling Carl; Hamsten Anders; Stemme Sten; Eriksson Per
CORPORATE SOURCE: Atherosclerosis Research Unit, Karolinska Hospital, Stockholm, Sweden.
SOURCE: The American journal of pathology, (2002 Sep) Vol. 161, No. 3, pp. 939-45.
Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 6 Sep 2002
Last Updated on STN: 28 Sep 2002
Entered Medline: 27 Sep 2002

AB Several groups of proteolytic enzymes are able to degrade components of the extracellular matrix. During atherosclerosis, matrix remodeling is believed to influence the migration and proliferation of cells within the plaque. In the present study, gene expression of several proteases and their inhibitors was analyzed during the development of atherosclerosis in apolipoprotein E-deficient (ApoE-/-) mice. Quantitative real-time

polymerase chain reaction was used to study gene expression of proteases after 10 and 20 weeks in ApoE-/- and C57BL/6 mice and in atherosclerotic lesions and nonaffected regions of the same ApoE-/- mouse. Some of the differentially expressed proteolytic enzymes were studied by immunohistochemistry. The matrix metalloproteinase (MMP)-9 and its inhibitor TIMP-1 were differentially expressed and the expression increased with time. Urokinase-type plasminogen activator showed no major expression. In contrast, cathepsins B, D, L, and S all showed strong and increased expression in ApoE-/- mice compared to C57BL/6 mice whereas the expression of their inhibitor, cystatin C, did not differ between the two mouse strains. The expression of cathepsins was mainly localized to the lesions and not to nonaffected regions of the aorta of ApoE-/- mice. Furthermore, cathepsin expression was similar to the expression of the macrophage marker macrosialin (CD68) although expression of cathepsins B, D, and L could be demonstrated in healthy C57BL/6 mice and in nonaffected vessel segments of atherosclerotic ApoE-/- mice. Cathepsin S mRNA expression was restricted to lesions of ApoE-/- mice. Furthermore, cathepsin S was the only cathepsin that was expressed in the media and absent in lipid-rich regions. All cathepsins studied showed intimal expression, the degree and localization of which differed between individual cathepsins. In conclusion, increased expression of several cathepsins in atherosclerotic lesions suggests that these proteases may participate in the remodeling of extracellular matrix associated with the atherosclerotic process.

L6 ANSWER 18 OF 78 MEDLINE on STN

ACCESSION NUMBER: 2002118348 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11815350
TITLE: CST3 genotype associated with exudative age related macular degeneration.
AUTHOR: Zurdel Jan; Finckh Ulrich; Menzer Gunnar; Nitsch Roger M; Richard Gisbert
CORPORATE SOURCE: Department of Ophthalmology, University Hospital Hamburg-Eppendorf, University of Hamburg, Germany.. zurdel@uke.uni-hamburg.de
SOURCE: The British journal of ophthalmology, (2002 Feb) Vol. 86, No. 2, pp. 214-9.
Journal code: 0421041. ISSN: 0007-1161.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 21 Feb 2002
Last Updated on STN: 8 Mar 2002
Entered Medline: 7 Mar 2002

AB AIMS: To determine whether allelic variants of the cystatin C gene CST3 are genetically associated with exudative age related macular degeneration (ARMD). Cystatin C is a cysteine protease inhibitor that regulates the activity of cathepsin S, a protease with central regulatory functions in retinal pigment epithelial cells. METHODS: CST3 of 167 patients with exudative ARMD was genotyped by using polymerase chain reaction of genomic DNA and restriction enzyme digestion with KspI and compared with those of 517 control subjects. Patients and controls were white. RESULTS: There was a significant difference in genotype counts between patients and controls (chi(2) = 7.158, df = 2; Fisher's exact test: p = 0.037). There was no significant difference in allele frequencies between patients and controls and between controls from Germany, Switzerland, Italy, and United States. The significant difference in genotype counts between patients and controls could be explained completely by an excess of the homozygous CST3

genotype B/B in patients with exudative ARMD (6.6%) over controls (2.3%), suggesting an odds ratio for ARMD in association with CST3 B/B of 2.97 (95% CI: 1.28-6.86). The results also suggest a stronger association of B/B with ARMD in males than in females. However, in both males and females there was a similar and significant effect of CST3 B/B on disease free survival assessed by Kaplan-Meier analysis. The mean disease free survival time in pooled males and females with genotypes A/A or A/B was 85 years (SE 1; 95% CI: 83-86) and 76 years (SE 2; 95% CI: 72-79) respectively in B/B homozygotes (log rank p = 0.0006). CONCLUSION: Genotyping data, the absence of a significant difference in allele frequencies between patients and controls, and survival analyses suggest an increased susceptibility for ARMD in CST3 B/B homozygotes. Therefore, CST3 B may be a recessive risk allele, significantly contributing to disease risk in up to 6.6% of German ARMD patients. Functional correlates of the allelic CST3 variants A and B remain to be investigated.

L6 ANSWER 19 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2001375476 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11433378
TITLE: Immunocompetent astrocytes and microglia display major differences in the processing of the invariant chain and in the expression of active cathepsin L and cathepsin S.
AUTHOR: Gresser O; Weber E; Hellwig A; Riese S; Regnier-Vigouroux A
CORPORATE SOURCE: Department of Neurobiology, Interdisziplinares Zentrum fur Neurowissenschaften, University of Heidelberg, Heidelberg, Germany.
SOURCE: European journal of immunology, (2001 Jun) Vol. 31, No. 6, pp. 1813-24.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 13 Aug 2001
Last Updated on STN: 20 Apr 2002
Entered Medline: 9 Aug 2001

AB The role of astrocytes and microglia as antigen-presenting cells in the brain is still controversial. In this study we have analyzed and compared aspects of the molecular machinery that underlies MHC class II trafficking in immunocompetent astrocytes and microglia. We show that IFN-gamma-stimulated microglia possess active cathepsin L and cathepsin S, and efficiently degrade the invariant chain, unlike IFN-gamma-stimulated astrocytes that express cathepsin L but not cathepsin S. The lack of cathepsin S proves to be dramatic for the antigen-presentation capacity of astrocytes, which is nearly abolished when these cells are stimulated by a combination of IFN-gamma and TNF-alpha. TNF-alpha indeed decreases cathepsin L activity as we show here, leading to alterations in invariant chain processing, and hence in MHC class II trafficking in astrocytes. Cystatin C inhibits cathepsin L activity in astrocytes, but does not regulate cathepsin L and cathepsin S activity in microglia. We therefore identify cathepsin L and cathepsin S as key components in the regulation of the immune potential of astrocytes and microglia, and provide evidence for a cell-specific regulation exerted by IFN-gamma and TNF-alpha on the expression and activity of cathepsins.

L6 ANSWER 20 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2001374723 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11431459
TITLE: Identification and localization of retinal cystatin C.
AUTHOR: Wasselius J; Hakansson K; Johansson K; Abrahamson M; Ehinger B
CORPORATE SOURCE: Department of Ophthalmology, Lund University Hospital, S-221 84 Lund, Sweden.. johan.wasselius@oft.lu.se
SOURCE: Investigative ophthalmology & visual science, (2001 Jul) Vol. 42, No. 8, pp. 1901-6.
Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 6 Aug 2001
Last Updated on STN: 6 Aug 2001
Entered Medline: 2 Aug 2001

AB PURPOSE. Cystatin C is a mammalian cysteine protease inhibitor, synthesized in various amounts by many kinds of cells and appearing in most body fluids. There are reports that it may be synthesized in the mammalian retina and that a cysteine protease inhibitor may influence the degradation of photoreceptor outer segment proteins. In the current study cystatin C was identified, quantitated, and localized in mouse, rat, and human retinas. METHODS. Enzyme-linked immunosorbent assay (ELISA), reverse transcription-polymerase chain reaction (RT-PCR), DNA sequencing, Western blot analysis, and immunohistochemistry have been used on mouse, rat, and human retinas (pigment epithelium included). RESULTS. Cystatin C is present in high concentrations in the normal adult rat retina, as it is throughout its postnatal development. Its concentration increases to a peak at the time when rat pups open their eyes and then remains at a high level. It is mainly localized to the pigment epithelium, but also to some few neurons of varying types in the inner retina. Cystatin C is similarly expressed in normal mouse and human retinas. CONCLUSIONS. Cystatin C was identified and the localization described in the retinas of rat, mouse, and human using several techniques. Cystatin C is known to efficiently inactivate certain cysteine proteases. One of them, cathepsin S, is present in the retinal pigment epithelium and affects the proteolytic processing by cathepsin D of diurnally shed photoreceptor outer segments. Hypothetically, it appears possible that retinal cystatin C, given its localization to the pigment epithelium and its ability to inhibit cathepsin S, could be involved in the regulation of photoreceptor degradation.

L6 ANSWER 21 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2001369313 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11301256
TITLE: Bm-CPI-2, a cystatin homolog secreted by the filarial parasite Brugia malayi, inhibits class II MHC-restricted antigen processing.
AUTHOR: Manoury B; Gregory W F; Maizels R M; Watts C
CORPORATE SOURCE: Department of Biochemistry, Wellcome Trust Biocentre, University of Dundee, DD1 5EH, Dundee, United Kingdom.
SOURCE: Current biology : CB, (2001 Mar 20) Vol. 11, No. 6, pp. 447-51.
Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 2 Jul 2001
Last Updated on STN: 2 Jul 2001
Entered Medline: 28 Jun 2001

AB While interference with the class I MHC pathway by pathogen-encoded gene products, especially those of viruses, has been well documented, few examples of specific interference with the MHC class II pathway have been reported. Potential targets for such interference are the proteases that remove the invariant chain chaperone and generate antigenic peptides. Indeed, recent studies indicate that immature dendritic cells express cystatin C to modulate cysteine protease activity and the expression of class II MHC molecules [1]. Here, we show that Bm-CPI-2, a recently discovered cystatin homolog produced by the filarial nematode parasite Brugia malayi (W. F. Gregory et al., submitted), inhibits multiple cysteine protease activities found in the endosomes/lysosomes of human B lymphocyte lines. CPI-2 blocked the hydrolysis of synthetic substrates favored by two different families of lysosomal cysteine proteases and blocked the in vitro processing of the tetanus toxin antigen by purified lysosome fractions. Moreover, CPI-2 substantially inhibited the presentation of selected T cell epitopes from tetanus toxin by living antigen-presenting cells. Our studies provide the first example of a product from a eukaryotic parasite that can directly interfere with antigen presentation, which, in turn, may suggest how filarial parasites might inactivate the host immune response to a helminth invader.

L6 ANSWER 22 OF 78 MEDLINE on STN
ACCESSION NUMBER: 2001285210 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11327826
TITLE: Human recombinant pro-dipeptidyl peptidase I (cathepsin C) can be activated by cathepsins L and S but not by autocatalytic processing.
AUTHOR: Dahl S W; Halkier T; Lauritzen C; Dolenc I; Pedersen J; Turk V; Turk B
CORPORATE SOURCE: Prozymex A/S, Dr. Neergaards Vej 17, DK-2970 Horsholm, Denmark.. swd@bioimage.dk
SOURCE: Biochemistry, (2001 Feb 13) Vol. 40, No. 6, pp. 1671-8. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 29 May 2001
Last Updated on STN: 20 Apr 2002
Entered Medline: 24 May 2001

AB Human dipeptidyl peptidase I was expressed in the insect cell/baculovirus system and purified in its active (rhDPPI) and precursor (pro-rhDPPI) forms. RhDPPI was very similar to the purified enzyme (hDPPI) with respect to glycosylation, enzymatic processing, oligomeric structure, CD spectra, and catalytic activity. The precursor, which was a dimer, could be activated approximately 2000-fold with papain. Cathepsin L efficiently activated pro-rhDPPI in vitro at pH 4.5 (k(app) approximately 2 x 10(3) min(-)(1) M(-)(1)), and two cleavage pathways were characterized. The initial cleavage was within the pro region between the residual pro part and the activation peptide. Subsequently, the activation peptide was cleaved from the catalytic region, and the latter was cleaved into the heavy and light chains. Alternatively, the pro region was first separated

from the catalytic region. Cathepsin S was a less efficient activating enzyme. Cathepsin B and rhDPPI did not activate pro-rhDPPI, and the proenzyme was incapable of autoactivation. Incubation of both pro-rhDPPI and rhDPPI with cathepsin D resulted in degradation. Cystatin C and stefins A and B inhibited rhDPPI with K(i) values in the nanomolar range (K(i) = 0.5-1.1 nM). The results suggest that cathepsin L could be an important activator of DPPI in vivo and that cathepsin D and possibly the cystatins may contribute to DPPI downregulation.

L6 ANSWER 23 OF 78 MEDLINE on STN
ACCESSION NUMBER: 1998319229 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9657147
TITLE: Developmental regulation of invariant chain proteolysis controls MHC class II trafficking in mouse dendritic cells.
AUTHOR: Pierre P; Mellman I
CORPORATE SOURCE: Department of Cell Biology, Yale University School of Medicine, New Haven, Connecticut 06520-8002, USA.
CONTRACT NUMBER: AI-34098 (United States NIAID)
GM-33904 (United States NIGMS)
SOURCE: Cell, (1998 Jun 26) Vol. 93, No. 7, pp. 1135-45.
Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 11 Aug 1998
Last Updated on STN: 11 Aug 1998
Entered Medline: 27 Jul 1998
AB Dendritic cells (DCs) developmentally regulate their capacity for antigen presentation by controlling the transport and surface expression of MHC class II molecules. These events reflect a developmental regulation of invariant (Ii) chain cleavage, most likely by the cysteine protease cathepsin S. In immature DCs, inefficient Ii chain cleavage due to low cathepsin S activity leads to the transport of class II-Ii chain complexes to lysosomes, while in mature DCs, elevated cathepsin S activity results in efficient delivery of class II alphabeta dimers to the plasma membrane. Cathepsin S is not controlled transcriptionally but by a novel mechanism involving alterations in the expression and localization of an endogenous cathepsin S inhibitor cystatin C. Thus, the ratio of cystatin C to cathepsin S in developing DCs helps to determine the fate of newly synthesized MHC class II molecules.

L6 ANSWER 24 OF 78 MEDLINE on STN
ACCESSION NUMBER: 1998215651 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9548757
TITLE: Cross-class inhibition of the cysteine proteinases cathepsins K, L, and S by the serpin squamous cell carcinoma antigen 1: a kinetic analysis.
AUTHOR: Schick C; Pemberton P A; Shi G P; Kamachi Y; Cataltepe S; Bartuski A J; Gornstein E R; Bromme D; Chapman H A; Silverman G A
CORPORATE SOURCE: Department of Pediatrics, The Harvard Medical School, Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: CA69331 (United States NCI)
CA73031 (United States NCI)

HD28475 (United States NICHD)
SOURCE: Biochemistry, (1998 Apr 14) Vol. 37, No. 15, pp. 5258-66.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 20 May 1998
Last Updated on STN: 20 Apr 2002
Entered Medline: 14 May 1998

AB The human squamous cell carcinoma antigens (SCCA) 1 and 2 are tandemly arrayed genes that encode two high-molecular-weight serine proteinase inhibitors (serpins). Although these proteins are 92% identical, differences in their reactive site loops suggest that they inhibit different types of proteinases. Our previous studies show that SCCA2 inhibits chymotrypsin-like serine proteinases [Schick et al. (1997) J. Biol. Chemical 272, 1849-1855]. We now show that, unlike SCCA2, SCCA1 lacks inhibitory activity against any of the more common types of serine proteinases but is a potent cross-class inhibitor of the archetypal lysosomal cysteine proteinases cathepsins K, L, and S. Kinetic analysis revealed that SCCA1 interacted with cathepsins K, L, and S at 1:1 stoichiometry and with second-order rate constants >/= 1 x 10(5) M-1 s-1. These rate constants were comparable to those obtained with the prototypical physiological cysteine proteinase inhibitor, cystatin C. Also relative to cystatin C, SCCA1 was a more potent inhibitor of cathepsin K-mediated elastolytic activity by forming longer lived inhibitor-proteinase complexes. The t1/2 of SCCA1-cathepsin S complexes was >1155 min, whereas that of cystatin C-cathepsin complexes was 55 min. Cleavage between the Gly and Ser residues of the reactive site loop and detection of a stable SCCA1-cathepsin S complex by sodium dodecyl sulfate-polyacrylamide gel electrophoresis suggested that the serpin interacted with the cysteine proteinase in a manner similar to that observed for typical serpin-serine proteinase interactions. These data suggest that, contingent upon their reactive site loop sequences, mammalian serpins, in general, utilize their dynamic tertiary structure to trap proteinases from more than one mechanistic class and that SCCA1, in particular, may be involved in a novel inhibitory pathway aimed at regulating a powerful array of lysosomal cysteine proteinases.

L6 ANSWER 25 OF 78 MEDLINE on STN
ACCESSION NUMBER: 1998189983 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9521728
TITLE: Structural basis for different inhibitory specificities of human cystatins C and D.
AUTHOR: Hall A; Ekiel I; Mason R W; Kasprzykowski F; Grubb A; Abrahamson M
CORPORATE SOURCE: Department of Clinical Chemistry, Institute of Laboratory Medicine, University of Lund, University Hospital, Sweden.
SOURCE: Biochemistry, (1998 Mar 24) Vol. 37, No. 12, pp. 4071-9.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804

ENTRY DATE: Entered STN: 7 May 1998
Last Updated on STN: 20 Apr 2002
Entered Medline: 30 Apr 1998

AB Human cystatins C and D share almost identical primary structures of two out of the three segments proposed to be of importance for enzyme interactions but have markedly different profiles for inhibition of the target cysteine peptidases, cathepsins B, H, L, and S. To investigate if the N-terminal binding regions of the inhibitors are responsible for the different inhibition profiles, and thereby confer biological selectivity, two hybrid cystatins were produced in Escherichia coli expression systems. In one hybrid, the N-terminal segment of cystatin C was placed on the framework of cystatin D, and the second was engineered with the N-terminal segment of cystatin D on the cystatin C scaffold. Truncated cystatin C and D variants, devoid of their N-terminal segments, were obtained by incubation with glycyl endopeptidase and isolated, in a second approach to assess the importance of the N-terminal binding regions for cystatin function and specificity. The affinities of the four cystatin variants for cathepsins B, H, L, and S were measured. By comparison with corresponding results for wild-type cystatins C and D, it was concluded (1) that both the N-terminal and framework part of the molecules significantly contribute to the observed differences in inhibitory activities of cystatins C and D and (2) that the N-terminal segment of cystatin C increases the inhibitory activity of cystatin D against cathepsin S and cathepsin L but results in decreased activity against cathepsin H. These differences in specificity were explained by the residues interacting with the S2 subsite of peptidases (Val- and Ala-10 in cystatin C and D, respectively). Also, removal of the N-terminal segment results in total loss of enzyme affinity for cystatin D but not for cystatin C. Therefore, structural differences in the framework parts, as well as in the N-terminal segments, are critical for both inhibitory specificity and potency. Homology modeling was used to identify residues likely responsible for the generally reduced inhibitory potency of cystatin D.

L6 ANSWER 26 OF 78 MEDLINE on STN
ACCESSION NUMBER: 1998149760 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9480898
TITLE: Amino acid substitutions in the N-terminal segment of cystatin C create selective protein inhibitors of lysosomal cysteine proteinases.
AUTHOR: Mason R W; Sol-Church K; Abrahamson M
CORPORATE SOURCE: Division of Developmental Biology, Nemours Research Programs, P.O. Box 269, Wilmington, DE 19899, USA.
SOURCE: The Biochemical journal, (1998 Mar 1) Vol. 330 (Pt 2), pp. 833-8.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 22 Apr 1998
Last Updated on STN: 20 Apr 2002
Entered Medline: 16 Apr 1998

AB We used site-directed mutagenesis to alter the specificity of human cystatin C, an inhibitor with a broad reactivity against cysteine proteinases. Nine cystatin C variants containing amino acid substitutions in the N-terminal (L9W, V10W, V10F and

V10R) and/or the C-terminal (W106G) enzyme-binding regions were designed and produced in Escherichia coli. It was discovered that the inhibition profile of the cystatin could be altered by changing residues 9 and 10, which are proposed to bind in the S3 and S2 substrate-binding pockets respectively of the enzymes. All of the variants with substitutions in the N-terminal segment displayed decreased binding to cathepsins B and H, indicating that the S3 and S2 pockets of these enzymes cannot easily accommodate large aromatic residues. The introduction of a charged residue into S2 (variant V10R) created a more specific inhibitor to distinguish cathepsin B from cathepsin H. Cathepsin L showed a preference for larger aromatic residues in S2. In contrast, cathepsin S preferred phenylalanine to valine in S2, but bound less tightly to the V10W cystatin variant. The latter variant proved to be valuable for discriminating between cathepsin L and cathepsin S (Ki 2.4 and 190 pM respectively). The equilibrium dissociation constant of the complex between cathepsin L and variant L9W/W106G showed little difference in affinity from that of the cathepsin L complex with the singly substituted W106G variant. In contrast, the L9W/W106G variant displayed increased specificity for cathepsin S with a Ki of 10 pM. Our results clearly indicate differences in the specificity of interaction between the N-terminal region of cystatin C and cathepsins B, H, L and S, and that, although cystatin C has evolved to be a good inhibitor of all of the mammalian cysteine proteinases, more specific inhibitors of the individual enzymes can be engineered.

L6 ANSWER 27 OF 78 MEDLINE on STN
ACCESSION NUMBER: 1996426544 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8828823
TITLE: Inhibition of bovine cathepsins L and S by stefins and cystatins.
AUTHOR: Leonardi A; Turk B; Turk V
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Jozef Stefan Institute, Ljubljana, Slovenia.
SOURCE: Biological chemistry Hoppe-Seyler, (1996 May) Vol. 377, No. 5, pp. 319-21.
Journal code: 8503054. ISSN: 0177-3593.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 20 Apr 2002
Entered Medline: 26 Dec 1996
AB Inhibition of bovine cathepsins L and S by bovine stefin B, human stefins A and B and cystatin C was studied under pseudo-first-order conditions by continuous fluorimetric assay. All inhibitors formed very tight complexes with the enzymes (Ki < or = 29 pM). The binding was reversible (kdiss = 0.52 - 16.7 x 10(-4) s-1) and very fast (kass = 2.8 - 6.2 x 10(7) M-1 S-1). Cystatin C was the strongest inhibitor of the enzymes, but the affinity was too tight to be measured accurately by this method. Consistently weaker inhibition of cathepsin S by all the stefins is apparent due mainly to the higher dissociation rate constants.

L6 ANSWER 28 OF 78 MEDLINE on STN
ACCESSION NUMBER: 1995352216 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7626231
TITLE: Regulation of the activity of lysosomal cysteine proteinases by pH-induced inactivation and/or endogenous

protein inhibitors, cystatins.
AUTHOR: Turk B; Bieth J G; Bjork I; Dolenc I; Turk D; Cimerman N; Kos J; Colic A; Stoka V; Turk V
CORPORATE SOURCE: Dept. Biochemistry and Molecular Biology, J. Stefan Institute, Ljubljana, Slovenia.
SOURCE: Biological chemistry Hoppe-Seyler, (1995 Apr) Vol. 376, No. 4, pp. 225-30.
Journal code: 8503054. ISSN: 0177-3593.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 21 Sep 1995
Last Updated on STN: 20 Apr 2002
Entered Medline: 7 Sep 1995

AB The kinetics of pH-induced inactivation of human cathepsins B and L was studied by conventional and stopped-flow methods. The inactivation of both enzymes was found to be an irreversible, first-order process. The inactivation rate constants increased exponentially with pH for both enzymes. From log kinac vs pH plots, 3.0 and 1.7 protons were calculated to be desorbed for pH-induced inactivation of cathepsins L and B. Cathepsin B was thus substantially more stable than cathepsin L (approximately 15-fold at pH 7.0 and 37 degrees C). Cathepsin B was efficiently inhibited by cystatin C at pH 7.4, whereas the inhibition by stefin B and high molecular weight kininogen was only moderate. In contrast, cathepsin L was efficiently inhibited by both chicken cystatin and stefin B at this pH kass approximately 3.3 x 10(7) m-1 s-1).

L6 ANSWER 29 OF 78 MEDLINE on STN
ACCESSION NUMBER: 1995197498 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7890620
TITLE: Structural basis for the biological specificity of cystatin C. Identification of leucine 9 in the N-terminal binding region as a selectivity-conferring residue in the inhibition of mammalian cysteine peptidases.
AUTHOR: Hall A; Hakansson K; Mason R W; Grubb A; Abrahamson M
CORPORATE SOURCE: Department of Clinical Chemistry, University of Lund, University Hospital, Sweden.
SOURCE: The Journal of biological chemistry, (1995 Mar 10) Vol. 270, No. 10, pp. 5115-21.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 27 Apr 1995
Last Updated on STN: 3 Mar 2000
Entered Medline: 14 Apr 1995

AB The structural basis for the biological specificity of human cystatin C has been investigated. Cystatin C and other inhibitors belonging to family 2 of the cystatin superfamily interact reversibly with target peptidases, seemingly by independent affinity contributions from a wedge-shaped binding region built from two loop-forming inhibitor segments and a binding region corresponding to the N-terminal segment of the inhibitor.

Human cystatin C variants with Gly substitutions for residues Arg-8, Leu-9, and/or Val-10 of the N-terminal binding region, and/or the evolutionarily conserved Trp-106 in the wedge-shaped binding region, were produced by site-directed mutagenesis and Escherichia coli expression. A total of 10 variants were isolated, structurally verified, and compared to wild-type cystatin C with respect to inhibition of the mammalian cysteine peptidases, cathepsins B, H, L, and S. Varying contributions from the N-terminal binding region and the wedge-shaped binding region to cystatin C affinity for the four target peptidases were observed. Interactions from the side chains of residues in the N-terminal binding region and Trp-106 are jointly responsible for the major part of cystatin C affinity for cathepsin L and are also of considerable importance for cathepsin B and H affinity. In contrast, for cathepsin S inhibition these interactions are of lesser significance, as reflected by a Ki value of 10(-8) M for the cystatin C variant devoid of Arg-8, Leu-9, Val-10, and Trp-106 side chains. The side chain of Val-10 is responsible for most of the affinity contribution from the N-terminal binding region, for all four enzymes. The contribution of the Arg-8 side chain is minor, but significant for cystatin C interaction with cathepsin B. The Leu-9 side chain confers selectivity to the inhibition of the target peptidases; it contributes to cathepsin B and L affinity by factors of 200 and 50, respectively, to cathepsin S binding by a factor of 5 only, and results in a 10-fold decreased affinity between cystatin C and cathepsin H.

L6 ANSWER 30 OF 78 MEDLINE on STN
ACCESSION NUMBER: 1994365015 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8083219
TITLE: Structural and functional characterization of two allelic variants of human cystatin D sharing a characteristic inhibition spectrum against mammalian cysteine proteinases.
AUTHOR: Balbin M; Hall A; Grubb A; Mason R W; Lopez-Otin C; Abrahamson M
CORPORATE SOURCE: Department of Clinical Chemistry, University of Lund, University Hospital, Sweden.
SOURCE: The Journal of biological chemistry, (1994 Sep 16) Vol. 269, No. 37, pp. 23156-62.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 21 Oct 1994
Last Updated on STN: 21 Oct 1994
Entered Medline: 11 Oct 1994
AB Human cystatin D is a novel member of the cystatin superfamily of cysteine proteinase inhibitors present in saliva and tears. Two alleles of the cystatin D gene (CST5), encoding protein variants with either Cys or Arg as residue 26 in their 122-residue polypeptide chains, are present in the population. Expression of the two alleles was investigated by immunochemical analyses of the secreted cystatin D in saliva from individuals homozygous for each of the two alleles, with results demonstrating that both are expressed at similar levels. The inhibitory characteristics of the two cystatin D variants were studied, by determination of dissociation equilibrium constants (Ki) for their complexes with papain and with the mammalian cysteine proteinases, cathepsins B, H, L, and S. The results demonstrate

that 1) cystatin D has a characteristic inhibition profile since it does not inhibit cathepsin B (Ki > 1 microM), and when compared to cystatin C and all other known cystatins it is a much poorer inhibitor of cathepsin L (mean Ki 25 nM) but binds cathepsin H and S relatively tightly (mean Ki values of 8.5 and 0.24 nM, respectively); and 2) the inhibitory activities of the two cystatin D variants are not significantly different, demonstrating that the presence of an extra cysteine residue in the cystatin D molecule affects neither the stability nor the functional activity of the inhibitor, thus explaining the widespread distribution of the Cys26-cystatin D encoding allele in the population. The inhibitory properties displayed by cystatin D suggest that it has a function in saliva as inhibitor of either endogenous or exogenous enzymes with cathepsin S- or H-like properties.

L6 ANSWER 31 OF 78 MEDLINE on STN
ACCESSION NUMBER: 1992198376 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1801734
TITLE: Tight-binding inhibition of cathepsin S by cystatins.
AUTHOR: Bromme D; Rinne R; Kirschke H
CORPORATE SOURCE: Institute of Biochemistry, Faculty of Medicine, Martin-Luther University, Halle (Saale), Germany.
SOURCE: Biomedica biochimica acta, (1991) Vol. 50, No. 4-6, pp. 631-5.
Journal code: 8304435. ISSN: 0232-766X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 9 May 1992
Last Updated on STN: 3 Feb 1997
Entered Medline: 23 Apr 1992
AB Human cystatins A, B and C were purified, and their inhibition efficiency was tested with the cysteine proteinase cathepsin S. Cathepsin S was strongly inhibited by cystatins A and B in the subnanomolar range and by cystatin C in the picomolar range. Two steps of inhibition of cathepsin S by the cystatins which involve slow binding are discussed.

L6 ANSWER 32 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2008:1044960 SCISEARCH
THE GENUINE ARTICLE: 335UZ
TITLE: Elastin- and collagen-rich human carotid plaques have increased levels of the cysteine protease inhibitor cystatin C
AUTHOR: Bengtsson, Eva (Reprint)
CORPORATE SOURCE: Lund Univ, Malmo Univ Hosp, Expt Cardiovasc Res Unit, Dept Clin Sci, Entrance 72, 91-12, SE-20502 Malmo, Sweden (Reprint)
AUTHOR: Goncalves, Isabel; Ares, Mikko P. S.; Moberg, Anna; Moses, Jonatan; To, Fong; Montan, Jonathan; Pedro, Luis M.; Dias, Nuno; Fernandes e Fernandes, Jose; Fredrikson, Gunilla Nordin; Nilsson, Jan; Jovinge, Stefan
CORPORATE SOURCE: Lund Univ, Expt Cardiovasc Res Unit, Dept Clin Sci, S-22100 Lund, Sweden; Malmo Univ Hosp, Dept Internal Med & Cardiol, Malmo, Sweden; Univ Lund Hosp, Dept Cardiol, Lund, Sweden; Lund Univ, Lund Stem Cell Ctr, Lund, Sweden;

Cardiovasc Inst Lisbon, Lisbon, Portugal
E-mail: eva.bengtsson@med.lu.se
COUNTRY OF AUTHOR: Sweden; Portugal
SOURCE: JOURNAL OF VASCULAR RESEARCH, (2008) Vol. 45, No. 5, pp. 395-401.
ISSN: 1018-1172.
PUBLISHER: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 24
ENTRY DATE: Entered STN: 28 Aug 2008
Last Updated on STN: 28 Aug 2008
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Cystatin C is a major inhibitor of the elastin- and collagen-degrading cysteine proteases and may therefore have an important role in preserving atherosclerotic plaque stability. In this study we analyzed the associations between human carotid plaque cystatin C expression and the plaque content of collagen and elastin. Methods: Thirty-one plaques were removed by endarterectomy and homogenized. Cystatin C levels were analyzed by densitometry of Western blots and elastin and collagen levels were determined colorimetrically. Results: The plaque content of cystatin C correlated with total elastin (r = 0.58, p = 0.001) and collagen (r = 0.50, p = 0.004), as well as with cross-linked forms of elastin (r = 0.42, p = 0.022) and collagen (r = 0.52, p = 0.003). Immunohistochemical analysis demonstrated that cystatin C colocalized with elastin and collagen. No correlation was seen between cystatin C and the amount of degraded elastin or collagen in plaques. Conclusion: The positive correlation between cystatin C levels and collagen and elastin levels in plaques supports the notion that cystatin C plays an important role in maintaining atherosclerotic plaque stability. Copyright (C) 2008 S. Karger AG, Basel.

L6 ANSWER 33 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2007:413884 SCISEARCH
THE GENUINE ARTICLE: 148ND
TITLE: Interaction between human cathepsins K, L, and S and elastins - Mechanism of elastinolysis and inhibition by macromolecular inhibitors
AUTHOR: Lenarcic, Brigita (Reprint)
CORPORATE SOURCE: Univ Ljubljana, Fac Chem & Chem Technol, Dept Chem & Biochem, Jamova 39, SI-1000 Ljubljana, Slovenia (Reprint)
AUTHOR: Novinec, Marko; Grass, Robert N.; Stark, Wendelin J.; Turk, Vito; Baici, Antonio
CORPORATE SOURCE: Univ Ljubljana, Fac Chem & Chem Technol, Dept Chem & Biochem, SI-1000 Ljubljana, Slovenia; Univ Zurich, Dept Biochem, CH-8057 Zurich, Switzerland; ETH, Dept Chem & Appl Biosci, Inst Chem & Bioengn, CH-8093 Zurich, Switzerland; Jozef Stefan Inst, Dept Biochem & Mol Biol, SI-1000 Ljubljana, Slovenia
E-mail: brigita.lenarcic@fkkt.uni-lj.si
COUNTRY OF AUTHOR: Slovenia; Switzerland
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (16 MAR 2007) Vol. 282, No. 11, pp. 7893-7902.
ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 62

ENTRY DATE: Entered STN: 26 Apr 2007
Last Updated on STN: 26 Apr 2007
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Proteolytic degradation of elastic fibers is associated with a broad spectrum of pathological conditions such as atherosclerosis and pulmonary emphysema. We have studied the interaction between elastins and human cysteine cathepsins K, L, and S, which are known to participate in elastinolytic activity in vivo. The enzymes showed distinctive preferences in degrading elastins from bovine neck ligament, aorta, and lung. Different susceptibility of these elastins to proteolysis was attributed to morphological differences observed by scanning electron microscopy. Kinetics of cathepsin binding to the insoluble substrate showed that the process occurs in two steps. The enzyme is initially adsorbed on the elastin surface in a nonproductive manner and then rearranges to form a catalytically competent complex. In contrast, soluble elastin is bound directly in a catalytically productive manner. Studies of enzyme partitioning between the phases showed that cathepsin K favors adsorption on elastin; cathepsin L prefers the aqueous environment, and cathepsin S is equally distributed among both phases. Our results suggest that elastinolysis by cysteine cathepsins proceeds in cycles of enzyme adsorption, binding of a susceptible peptide moiety, hydrolysis, and desorption. Alternatively, the enzyme may also form a new catalytic complex without prior desorption and re-adsorption. In both cases the active center of the enzymes remains at least partly accessible to inhibitors. Elastinolytic activity was readily abolished by cystatins, indicating that, unlike enzymes such as leukocyte elastase, pathological elastinorlytic cysteine cathepsins might represent less problematic drug targets. In contrast, thyropins were relatively inefficient in preventing elastincilysis by cysteine cathepsins.

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ACCESSION NUMBER: 2007:174881 SCISEARCH
THE GENUINE ARTICLE: 127PE
TITLE: Elastolytic cathepsin induction/activation system exists in myocardium and is upregulated in hypertensive heart failure
AUTHOR: Cheng, Xian Wu (Reprint)
CORPORATE SOURCE: Nagoya Univ, Sch Med, Dept Cardiovasc Genome Sci, Showa Ku, 65 Tsuruma Cho, Nagoya, Aichi 4668550, Japan (Reprint)
AUTHOR: Obata, Koji; Kuzuya, Masafumi; Izawa, Hideo; Nakamura, Kae; Asai, Eri; Nagasaka, Tetsuro; Saka, Masako; Kimata, Takahiro; Noda, Akiko; Nagata, Kohzo; Jin, Hai; Shi, Guo-Ping; Iguchi, Akihisa; Murohara, Toyoaki; Yokota, Mitsuhiro
CORPORATE SOURCE: Nagoya Univ, Sch Med, Dept Cardiovasc Genome Sci, Showa Ku, Nagoya, Aichi 4668550, Japan; Nagoya Univ, Grad Sch Med, Dept Geriatr, Nagoya, Aichi, Japan; Nagoya Univ, Grad Sch Med, Dept Cardiol, Nagoya, Aichi, Japan; Nagoya Univ, Grad Sch Med, Dept Clin Pathophysiol, Nagoya, Aichi, Japan; Nagoya Univ, Sch Hlth Sci, Dept Med Technol, Nagoya, Aichi, Japan; Harvard Univ, Sch Med, Brigham & Womens Hosp, Dept Cardiovasc Med, Boston, MA USA; Yanbian Univ, Dept Cardiol, Coll Med, Yanji, Jilin, Peoples R China
E-mail: xianwu@med.nagoya-u.ac.jp
COUNTRY OF AUTHOR: Japan; USA; Peoples R China
SOURCE: HYPERTENSION, (NOV 2006) Vol. 48, No. 5, pp. 979-987. ISSN: 0194-911X.
PUBLISHER: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
DOCUMENT TYPE: Article; Journal

LANGUAGE: English
REFERENCE COUNT: 42
ENTRY DATE: Entered STN: 22 Feb 2007
Last Updated on STN: 22 Feb 2007
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cathepsins are cysteine proteases that participate in various types of tissue remodeling. However, their expressions during myocardial remodeling have not been examined. In this study, we investigated their expressions in the left ventricular (LV) myocardium of rats and humans with hypertension-induced LV hypertrophy or heart failure (HF). Real-time PCR and immunoblot analysis revealed that the abundance of cathepsin S mRNA or protein in the LV tissues was greater in rats or humans with HF than in those with hypertrophy or in control subjects. Immunostaining showed that cathepsin S was localized predominantly to cardiac myocytes and coronary vascular smooth muscle cells, but also overlapped in part with macrophages. Elastic lamina fragmentations significantly increased in the LV intramyocardial coronary arteries of HF rats. The amount of elastolytic activity in the extract of the LV myocardium was markedly increased for HF rats compared with controls, and this activity was mostly because of cathepsin S. Although the amount of elastin mRNA was increased in the LV myocardium of HF rats, the area of interstitial elastin was not. The expression of interleukin 1 beta was increased in the LV myocardium of HF rats, and this cytokine was found to increase the expression and activity of cathepsin S in cultured neonatal cardiomyocytes. These results suggest that cathepsin S participates in pathological LV remodeling associated with hypertension-induced HF. This protease is, thus, a potential target for therapeutics aimed at preventing or reversing cardiac remodeling.

L6 ANSWER 35 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:501971 SCISEARCH
THE GENUINE ARTICLE: 041LX
TITLE: Chronic inflammation, immune response, and infection in abdominal aortic aneurysms
AUTHOR: Lindholt J S (Reprint)
CORPORATE SOURCE: Viborg Sygehus, Dept Vasc Surg, Vasc Res Unit, POB 130, DK-8800 Viborg, Denmark (Reprint)
AUTHOR: Shi G P
CORPORATE SOURCE: Viborg Sygehus, Dept Vasc Surg, Vasc Res Unit, DK-8800 Viborg, Denmark; Harvard Univ, Sch Med, Brigham & Womens Hosp, Dept Med, Boston, MA 02115 USA
E-mail: jes.s.lindholt@sygehusviborg.dk
COUNTRY OF AUTHOR: Denmark; USA
SOURCE: EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY, (MAY 2006) Vol. 31, No. 5, pp. 453-463.
ISSN: 1078-5884.
PUBLISHER: W B SAUNDERS CO LTD, 32 JAMESTOWN RD, LONDON NW1 7BY, ENGLAND.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 87
ENTRY DATE: Entered STN: 1 Jun 2006
Last Updated on STN: 1 Jun 2006
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Abdominal aortic aneurysms (AAA) are associated with atherosclerosis, transmural degenerative processes, neovascularization, decrease in content of vascular smooth muscle cells, and a chronic infiltration, mainly located in the outer aortic wall.

The chronic infiltration consists mainly of macrophages, lymphocytes,

and plasma cells. The dominant cells are Th2 restricted CD3+ lymphocytes expressing interleukine 4, 5, 8, and 10, and tumor necrosis factor-alpha for regulation of the local immune response. They also produce interferon-gamma and CD40 ligand to stimulate surrounding cells to produce matrix metalloproteases and cysteine proteases for aortic matrix remodeling. The lymphocyte activation may be mediated by microorganisms as well as autoantigens generated from vascular structural proteins, perhaps through molecular mimicry. As in autoimmune diseases, the risk of AAA is increased by certain genotypes concerning human leucocyte antigen class If. These types are also associated with increased aneurysmal inflammation indicating a genetic susceptibility to aortic inflammation.

Chlamydia pneumoniae is often detected in AAA but the validity of the methods can be questioned, and two small antibiotic trials have been disappointing. However, serum antibodies against C. pneumoniae have been associated with AAA growth and cross-react with AAA wall proteins. Thus, immune responses mediated by microorganisms and autoantigens may play a pivotal role in AAA pathogenesis.

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ACCESSION NUMBER: 2005:984481 SCISEARCH
THE GENUINE ARTICLE: 969JX
TITLE: Lack of the cysteine protease inhibitor cystatin C promotes atherosclerosis in apolipoprotein E-deficient mice
AUTHOR: Bengtsson E (Reprint)
CORPORATE SOURCE: Lund Univ, Malmo Univ Hosp, Wallenberg Lab, Dept Clin Sci, Ing 46, S-20502 Malmo, Sweden (Reprint)
AUTHOR: To F; Hakansson K; Grubb A; Branen L; Nilsson J; Jovinge S
CORPORATE SOURCE: Lund Univ, Malmo Univ Hosp, Wallenberg Lab, Dept Clin Sci, S-20502 Malmo, Sweden; Lund Univ, Univ Lund Hosp, Dept Cardiol, Coronary Program, Heart & Lung Div, Lund, Sweden; Lund Univ, Lund Strateg Res Ctr Stem Cell Biol & Cell Therap, Lund, Sweden
E-mail: eva.bengtsson@med.lu.se
COUNTRY OF AUTHOR: Sweden
SOURCE: ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY, (OCT 2005) Vol. 25, No. 10, pp. 2151-2156.
ISSN: 1079-5642.
PUBLISHER: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3261 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 27
ENTRY DATE: Entered STN: 13 Oct 2005
Last Updated on STN: 13 Oct 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective - Degradation of extracellular matrix plays an important role in growth and destabilization of atherosclerotic plaques. Cystatin C, inhibitor of the collagen- and elastin-degrading cysteine proteases of the cathepsin family, is produced by virtually all cell types. It is present in the normal artery wall but severely reduced in human atherosclerotic lesions.

Methods and Results - To determine the functional role of cystatin C in atherosclerosis, we crossed cystatin C - deficient (cysC(-/-)) mice with apolipoprotein E - deficient (apoE(-/-)) mice. After 25 weeks of atherogenic diet, mice lacking apoE and cystatin C (cysC(-/-) apoE(-/-)) had larger subvalvular plaques compared with cysC(+/+) apoE(-/-) mice (766 000 +/- 20 000 mu m(2) per section versus 662 000 +/- 19 000 mu m(2) per section; P = 0.001), suggesting an atheroprotective role of cystatin C. The plaques from

cysC(-/-) apoE(-/-) mice were characterized by increased total macrophage content. To determine which cellular source is important for the antiatherosclerotic effect of cystatin C, we performed bone marrow transplantations. ApoE(-/-) mice were transplanted with either cysC(-/-) apoE(+/+) or cysC(+/+) apoE(-/-) bone marrow. No significant differences in plaque area, macrophage, collagen, or lipid content of subvalvular lesions between the 2 groups were detected. Conclusions - The result suggests that the protective role of cystatin C in atherosclerosis is dependent primarily on its expression in nonhematopoietic cell types.

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ACCESSION NUMBER: 2005:718812 SCISEARCH
THE GENUINE ARTICLE: 942OI
TITLE: Differentiation- and maturation-dependent content, localization, and secretion of cystatin C in human dendritic cells
AUTHOR: Zavasnik-Bergant T (Reprint)
CORPORATE SOURCE: Jozef Stefan Inst, Dept Biochem & Mol Biol, Jamova 39, SI-1000 Ljubljana, Slovenia (Reprint)
AUTHOR: Repnik U; Schweiger A; Romih R; Jeras M; Turk V; Kos J
CORPORATE SOURCE: Jozef Stefan Inst, Dept Biochem & Mol Biol, SI-1000 Ljubljana, Slovenia; Blood Transfus Ctr Slovenia, Tissue Typing Ctr, Ljubljana, Slovenia; Univ Ljubljana, Fac Med, Inst Cell Biol, Ljubljana, Slovenia; Univ Ljubljana, Fac Pharm, Ljubljana, Slovenia
E-mail: tina.zavasnik@ijs.si
COUNTRY OF AUTHOR: Slovenia
SOURCE: JOURNAL OF LEUKOCYTE BIOLOGY, (JUL 2005) Vol. 78, No. 1, pp. 122-134.
ISSN: 0741-5400.
PUBLISHER: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41
ENTRY DATE: Entered STN: 22 Jul 2005
Last Updated on STN: 22 Jul 2005

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Antigen-presenting cells (APC) play a pivotal role in the initiation of the T cell-mediated and antigen-specific immune response. The suggested role of endogenous inhibitor cystatin C (CyC) is to modulate cysteine proteases (cathepsins) present in human APC. To test this hypothesis, dendritic cells (DC) were generated in vitro from isolated monocytes, and changes in content, localization, and secretion of CyC and cathepsins S, L, and H (CatS, -L, and -H, repsectively) were followed in response to interleukin-4, enabling monocyte differentiation, and to tumor necrosis factor alpha (TNF-alpha), enabling DC maturation. A large increase in intracellular CyC accompanied the differentiation of monocytes to immature DC, also shown by strong immunolabelling of Golgi in immature DC. On DC maturation, intracellular CyC levels decreased, and CyC was mostly absent from the Golgi. On prolonged incubation of mature DC with TNF-alpha, CyC was found located in the proximity of the plasma membrane, indicating that the transport of CyC from Golgi was not blocked as the result of the arrested exocytosis in mature DC. The secretion of CyC ceased, consistent with the peak of the surface expression of phenotypic markers (CD40, CD54, CD80, CD83, CD86, and major histocompatibility complex class H), characteristic for the mature DC stage, whereas the secretion of cathepsins did not correlate with the maturation stage. The difference in localization of CyC and of CatS, -L, and -H in immature and mature DC shows that the regulatory potential of

CyC toward CatS, -L, and -H inside DC is limited. However, these interactions may occur extracellularly in lymph, as suggested by the large excess of CyC over secreted CatS, -L, and -H, and they may facilitate DC. on to lymph nodes.

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ACCESSION NUMBER: 2005:620989 SCISEARCH
THE GENUINE ARTICLE: 934AM
TITLE: Changes in the spatial expression of genes with aging in the mouse RPE/choroid
AUTHOR: Hjelmeland L M (Reprint)
CORPORATE SOURCE: Univ Calif Davis, Sch Med, Vitreoretinal Res Lab, Dept Biol Chem & Ophthalmol, 1 Shields Ave, Davis, CA 95616 USA (Reprint)
AUTHOR: Ogawa T; Boylan S A; Oltjen S L
CORPORATE SOURCE: Univ Calif Davis, Sch Med, Vitreoretinal Res Lab, Dept Biol Chem & Ophthalmol, Davis, CA 95616 USA
E-mail: lmhjelmeland@ucdavis.edu
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR VISION, (1 JUN 2005) Vol. 11, No. 45, pp. 380-386.
ISSN: 1090-0535.
PUBLISHER: MOLECULAR VISION, C/O JEFF BOATRIGHT, LAB B, 5500 EMORY EYE CENTER, 1327 CLIFTON RD, N E, ATLANTA, GA 30322 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 21
ENTRY DATE: Entered STN: 23 Jun 2005
Last Updated on STN: 23 Jun 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose: We recently used microarray and reverse transcriptase PCR (RT-PCR) analysis to show an upregulation of cathepsin S (CatS) and glutathione peroxidase 3 (GPX3) in the aging mouse RPE/choroid. To evaluate the mRNA distribution and levels in the RPE and choroid, in situ hybridizations were performed.

Methods: Eye sections from 2-month-old and 24-month-old C57BL/6 mice were probed for CatS or GPX3 mRNA by in situ hybridization. The ratio of mRNA labeled cells to total cells counted per section was compared between the two age groups for the RPE and choroid separately.

Results: The CatS labeled RPE cell ratio increased significantly with age. The GPX3 labeled RPE cell ratio did not increase with age.

Conclusions: The increases in mRNA levels for CatS and GPX3 found in the aging C57BL/6 RPE/choroid appear to represent an increase in both the numbers of cells expressing these messages and an increase in the level of expression in individual cells.

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ACCESSION NUMBER: 2005:273227 SCISEARCH
THE GENUINE ARTICLE: 902ZM
TITLE: Inhibitory properties of cystatin F and its localization in U937 promonocyte cells
AUTHOR: Langerholc T (Reprint)
CORPORATE SOURCE: Jozef Stefan Inst, Dept Biochem & Mol Biol, Ljubljana, Slovenia (Reprint)
AUTHOR: Zavasnik-Bergant V; Turk B; Turk V; Abrahamson M; Kos J
CORPORATE SOURCE: Lund Univ, Inst Lab Med, Dept Clin Chem, S-22100 Lund, Sweden; Univ Ljubljana, Fac Pharm, Dept Pharmaceut Biol, Ljubljana 61000, Slovenia
E-mail: tomaz.langerholc@ijs.si
COUNTRY OF AUTHOR: Slovenia; Sweden

SOURCE: FEBS JOURNAL, (MAR 2005) Vol. 272, No. 6, pp. 1535-1545. ISSN: 1742-464X.
PUBLISHER: BLACKWELL PUBLISHING LTD, 9600 GARSINGTON RD, OXFORD OX4 2DG, OXON, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 49
ENTRY DATE: Entered STN: 18 Mar 2005
Last Updated on STN: 18 Mar 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cystatin F is a recently discovered type II cystatin expressed almost exclusively in immune cells. It is present intracellularly in lysosome-like vesicles, which suggests a potential role in regulating papain-like cathepsins involved in antigen presentation. Therefore, interactions of cystatin F with several of its potential targets, cathepsins F, K, V, S, H, X and C, were studied in vitro. Cystatin F tightly inhibited cathepsins F, K and V with K-i values ranging from 0.17 nm to 0.35 nm, whereas cathepsins S and H were inhibited with 100-fold lower affinities (K-i approximate to 30 nm). The exopeptidases, cathepsins C and X were not inhibited by cystatin F. In order to investigate the biological significance of the inhibition data, the intracellular localization of cystatin F and its potential targets, cathepsins B, H, L, S, C and K, were studied by confocal microscopy in U937 promonocyte cells. Although vesicular staining was observed for all the enzymes, only cathepsins H and X were found to be colocalized with the inhibitor. This suggests that cystatin F in U937 cells may function as a regulatory inhibitor of proteolytic activity of cathepsin H or, more likely, as a protection against cathepsins misdirected to specific cystatin F containing endosomal/lysosomal vesicles. The finding that cystatin F was not colocalized with cystatin C suggests distinct functions for these two cysteine protease inhibitors in U937 cells.

L6 ANSWER 40 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:201317 SCISEARCH
THE GENUINE ARTICLE: 898PG
TITLE: Cystatin C deficiency increases elastic lamina degradation and aortic dilatation in apolipoprotein E-null mice
AUTHOR: Shi G P (Reprint)
CORPORATE SOURCE: NRB-7, 77 Ave Louis Pasteur, Boston, MA 02115 USA (Reprint)
AUTHOR: Sukhova G K; Wang B; Libby P; Pan J H; Zhang Y; Grubb A; Fang K; Chapman H A
CORPORATE SOURCE: Harvard Univ, Sch Med, Brigham & Womens Hosp, Dept Med, Donald W Reynolds Cardiovasc Clin Res Ctr, Boston, MA USA; Univ Calif San Francisco, Dept Med, San Francisco, CA 94143 USA; Lund Univ, Dept Clin Chem, S-22100 Lund, Sweden
E-mail: gshi@rics.bwh.harvard.edu
COUNTRY OF AUTHOR: USA; Sweden
SOURCE: CIRCULATION RESEARCH, (18 FEB 2005) Vol. 96, No. 3, pp. 368-375.
ISSN: 0009-7330.
PUBLISHER: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 31
ENTRY DATE: Entered STN: 3 Mar 2005
Last Updated on STN: 3 Mar 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The pathogenesis of atherosclerosis and abdominal aortic aneurysm involves substantial proteolysis of the arterial extracellular matrix. The lysosomal cysteine proteases can exert potent elastolytic and collagenolytic activity. Human atherosclerotic plaques have increased cysteine protease content and decreased levels of the endogenous inhibitor cystatin C, suggesting an imbalance that would favor matrix degradation in the arterial wall. This study tested directly the hypothesis that impaired expression of cystatin C alters arterial structure. Cystatin C-deficient mice (Cyst C-/-) were crossbred with apolipoprotein E-deficient mice (ApoE(-/-)) to generate cystatin C and apolipoprotein E-double deficient mice (Cyst C-/- ApoE(-/-)). After 12 weeks on an atherogenic diet, cystatin C deficiency yielded significantly increased tunica media elastic lamina fragmentation, decreased medial size, and increased smooth muscle cell and collagen content in aortic lesions of ApoE(-/-) mice. Cyst C-/- ApoE(-/-) mice also showed dilated thoracic and abdominal aortae compared with control ApoE(-/-) mice, although atheroma lesion size, intimal macrophage accumulation, and lipid core size did not differ between these mice. These findings demonstrate directly the importance of cysteine protease/protease inhibitor balance in dysregulated arterial integrity and remodeling during experimental atherogenesis.

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ACCESSION NUMBER: 2005:156633 SCISEARCH
THE GENUINE ARTICLE: 894IF
TITLE: Cystatin C-positive macrophages and dendritic cells in the rat incisor pulp
AUTHOR: Nishikawa S (Reprint)
CORPORATE SOURCE: Tsurumi Univ, Sch Dent Med, Dept Biol, Tsurumi Ku, 2-1-3 Tsuruni, Yokohama, Kanagawa 2308501, Japan (Reprint)
AUTHOR: Nishikawa S (Reprint)
CORPORATE SOURCE: Tsurumi Univ, Sch Dent Med, Dept Biol, Tsurumi Ku, Yokohama, Kanagawa 2308501, Japan
E-mail: nishikawa-s@tsurumi-u.ac.jp
COUNTRY OF AUTHOR: Japan
SOURCE: ACTA HISTOCHEMICA ET CYTOCHEMICA, (2004) Vol. 37, No. 5, pp. 313-318.
ISSN: 0044-5991.
PUBLISHER: JAPAN SOC HISTOCHEM CYTOCHEM, NAKANISHI PRINTING CO SHIMOTACHIURI-OGAWA KAMIKYOKU, KYOTO, 602, JAPAN.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 27
ENTRY DATE: Entered STN: 24 Feb 2005
Last Updated on STN: 24 Feb 2005

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Localization of cystatin C, an endogenous cysteine protease inhibitor, was examined in the dental pulp of rat incisors using immunofluorescence microscopy. Based on double labeling with ED1 and anti-cystatin C antibodies, it was determined that anti cystatin C-labeled cells were macrophages and/or dendritic cells. Furthermore, cells in the incisor pulp were characterized by triple labeling with anti-cystatin C antibodies, ED2 antibodies for resident macrophages and OX6 antibodies for MHC class II antigens. Three cysteine proteases, cathepsin B, L and S, were also examined with immunocytochemistry. The results showed, firstly, that cystatin C single-positive cells were localized in early apical pulp, and that these cells were presumably immature macrophages invading newly formed dental pulp. Secondly, about half of OX6(+) cells in the middle and incisal pulp were ED2(+),

indicating that resident macrophages in addition to dendritic cells contribute to antigen surveillance via MHC Class II presentation. Thirdly, cathepsin S was present in cystatin C+ cells, and therefore they may be involved in formation of proteolytic environment in whole dental pulp. In conclusion, cystatin C-positive macrophages and possibly dendritic cells may play a role in regulating the proteolytic environment of the dental pulp as well as in immunological surveillance.

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ACCESSION NUMBER: 2004:252758 SCISEARCH
THE GENUINE ARTICLE: 800UI
TITLE: Human evidence that the cystatin C gene is implicated in focal progression of coronary artery disease
AUTHOR: Eriksson P (Reprint)
CORPORATE SOURCE: Karolinska Inst, Karolinska Hosp, King Gustaf V Res Inst, Atherosclerosis Res Unit, S-17176 Stockholm, Sweden (Reprint)
AUTHOR: Deguchi H; Samnegard A; Lundman P; Boquist S; Tornvall P; Ericsson C G; Bergstrand L; Hansson L O; Ye S; Hamsten A
CORPORATE SOURCE: Karolinska Inst, Karolinska Hosp, Dept Med, Cardiol Unit, Stockholm, Sweden; Karolinska Inst, Karolinska Hosp, Dept Surg, Div Clin Chem & Blood Coagulat, Stockholm, Sweden; Karolinska Inst, Danderyd Hosp, Dept Med, Cardiol Unit, S-18288 Danderyd, Sweden; Karolinska Inst, Danderyd Hosp, Dept Radiol, S-18288 Danderyd, Sweden; Univ Southampton, Sch Med, Div Human Genet, Southampton, Hants, England
COUNTRY OF AUTHOR: Sweden; England
SOURCE: ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY, (MAR 2004) Vol. 24, No. 3, pp. 551-557. ISSN: 1079-5642.
PUBLISHER: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 31
ENTRY DATE: Entered STN: 26 Mar 2004
Last Updated on STN: 26 Mar 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective - Overexpression of elastolytic cysteine and aspartic proteases, known as cathepsins, is implicated in atherogenesis. The potential significance of imbalance in expression between cathepsins and their inhibitor cystatin C in cardiovascular disease has been highlighted by the demonstration of cystatin C deficiency in human atherosclerosis and abdominal aortic aneurysms.

Methods and Results - We identified and characterized physiologically relevant polymorphisms in the promoter region of the cystatin C gene that influence cystatin C production and used these polymorphisms as a tool to examine the significance of cystatin C in coronary atherosclerosis in vivo in humans. Seven polymorphisms, all in strong-linkage disequilibrium, were identified in the cystatin C gene, of which 2 promoter polymorphisms (- 82G/ C and - 78T/ G) were functional in vitro in electromobility shift and transient transfection assays. Genotyping of 1105 individuals (237 survivors of a first myocardial infarction before age 60 and 2 independent groups comprising a total of 868 healthy individuals) revealed that the plasma cystatin C concentration was significantly lower in carriers of the mutant haplotype. Furthermore, the mutant haplotype was associated with a higher average number of stenoses per coronary artery segment in unselected

postinfarction patients (N = 237) undergoing routine coronary angiography. Conclusions - These results provide human evidence for an important role of cystatin C in coronary artery disease.

L6 ANSWER 43 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:518885 SCISEARCH
THE GENUINE ARTICLE: 564GY
TITLE: A second locus for very-late-onset Alzheimer disease: A genome scan reveals linkage to 20p and epistasis between 20p and the amyloid precursor protein region
AUTHOR: Olson J M (Reprint)
CORPORATE SOURCE: Case Western Reserve Univ, Dept Epidemiol & Biostat, Rammelkamp Ctr Educ & Res, 2500 MetroHlth Drive, R258, MetroHlth Campus, Cleveland, OH 44109 USA (Reprint)
AUTHOR: Goddard K A B; Dudek D M
CORPORATE SOURCE: Case Western Reserve Univ, Dept Epidemiol & Biostat, Rammelkamp Ctr Educ & Res, Cleveland, OH 44109 USA
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF HUMAN GENETICS, (JUL 2002) Vol. 71, No. 1, pp. 154-161.
ISSN: 0002-9297.
PUBLISHER: UNIV CHICAGO PRESS, 1427 E 60TH ST, CHICAGO, IL 60637-2954 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 33
ENTRY DATE: Entered STN: 12 Jul 2002
Last Updated on STN: 12 Jul 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB We used a covariate-based linkage method to reanalyze genome scan data from affected sibships collected by the Alzheimer Disease (AD) Genetics Initiative of the National Institute of Mental Health. As reported in an earlier article, the amyloid-beta precursor protein (APP) region is strongly linked to affected sib pairs of the oldest current age (i.e., age either at last exam or at death) who lack E4 alleles at the apolipoprotein E (ApoE) locus. We now report that a region on 20p shows the same pattern. A model that includes current age and the number of E2 alleles as covariates gives a LOD score of 4.1. The signal on 20p is near the location of the gene coding for cystatin-C, previously shown to be associated with late-onset AD and to codeposit with APP in the brains of patients with AD. Two-locus analysis provides evidence of strong epistasis between 20p and the APP region, limited to the oldest age group and to those lacking ApoE4 alleles. We speculate that high-risk polymorphisms in both regions produce a biological interaction between these two proteins that increases susceptibility to a very-late-onset form of AD.

L6 ANSWER 44 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:237440 SCISEARCH
THE GENUINE ARTICLE: 529RC
TITLE: Recent developments of cathepsin inhibitors and their selectivity
AUTHOR: Kim W (Reprint)
CORPORATE SOURCE: Kosin Univ, Coll Med, Dept Pharmacol, Pusan 602702, South Korea (Reprint)
AUTHOR: Kang K
COUNTRY OF AUTHOR: South Korea
SOURCE: EXPERT OPINION ON THERAPEUTIC PATENTS, (MAR 2002) Vol. 12, No. 3, pp. 419-432.
ISSN: 1354-3776.

PUBLISHER: ASHLEY PUBLICATIONS LTD, UNITEC HOUSE, 3RD FL, 2 ALBERT PLACE, FINCHLEY CENTRAL, LONDON N3 1QB, ENGLAND.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 94
ENTRY DATE: Entered STN: 29 Mar 2002
Last Updated on STN: 29 Mar 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cathepsins play an important role in the degradation of host connective tissues, the generation of bioactive proteins and antigen processing. They have been implicated in osteoporosis, muscular dystrophy, rheumatoid arthritis, bronchitis, emphysema, viral infection, cancer metastasis and neurodegenerative diseases, such as Alzheimer's disease and Huntington's disease. Recently, increased interest in cathepsin inhibitors has been generated with potential therapeutic targets, such as cathepsin K or cathepsin L for osteoporosis and cathepsin S for immune modulation. Of the 53 patents assessed in this review, granted between March 1998 and February 2001, there were 40 patents related to cysteine proteinase inhibitors, 7 related to aspartic proteinase inhibitors and 6 related to serine proteinase inhibitors. Of the 40 patents, 14 disclosed the novel compounds that were more selective against cathepsin K or cathepsin S than cathepsin B and cathepsin L. The compounds, showing experimental evidences, were evaluated and their biological activities in animal models determined. However, only 4 patents presented significant results in vivo. These patents may be a basis for promoting further evaluation and developing second generation cathepsin inhibitors.

L6 ANSWER 45 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:897133 SCISEARCH
THE GENUINE ARTICLE: 490HM
TITLE: Cystatin C deficiency is associated with the progression of small abdominal aortic aneurysms
AUTHOR: Lindholt J S (Reprint)
CORPORATE SOURCE: Laerkevej 11, DK-8900 Randers, Denmark (Reprint)
AUTHOR: Erlandsen E J; Henneberg E W
CORPORATE SOURCE: Viborg Kjellerup Cty Hosp, Dept Vasc Surg, Viborg, Denmark; Viborg Kjellerup Cty Hosp, Dept Clin Biochem, Viborg, Denmark
COUNTRY OF AUTHOR: Denmark
SOURCE: BRITISH JOURNAL OF SURGERY, (NOV 2001) Vol. 88, No. 11, pp. 1472-1475.
ISSN: 0007-1323.
PUBLISHER: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 15
ENTRY DATE: Entered STN: 21 Nov 2001
Last Updated on STN: 21 Nov 2001
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: The cysteine protease inhibitor cystatin C may play a role in the development and progression of abdominal aortic aneurysms (AA-As).

Methods: From a mass screening trial of men aged 65-73 years, 151 small AAAs were followed for a mean of 2.9 years. Of these patients, 142 had serum samples taken to determine the levels of cystatin C, creatinine and C-reactive protein (CRP).

Results: Serum cystatin C concentration correlated negatively with AAA size (r = -0.22 (95 per cent confidence interval (c.i.) -0.59 to -0.02)) and annual expansion rate (r = -0.24 (95

per cent c.i. -0.75 to -0.05)), persisting after adjustment for renal function, smoking, diastolic blood pressure, CRP, age and AAA size. Creatinine clearance and CRP did not correlate with size or expansion rate. Thirty-one AAAs had expanded to over 50 mm, when operation was recommended. The serum level of cystatin C was a significant predictor of this occurrence, with a sensitivity and specificity of 61 and 57 per cent respectively. However, initial AAA size had the optimal sensitivity and specificity (both 81 per cent) in this regard.

Conclusion: Deficiency of cystatin C was associated with increased aneurysm size and expansion rate, possibly due to lack of inhibition of cysteine proteases.

L6 ANSWER 46 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:815480 SCISEARCH
THE GENUINE ARTICLE: 478VD
TITLE: Circadian and concentration profile of cathepsin S in sera from healthy subjects and asthmatic patients
AUTHOR: Cimerman N (Reprint)
CORPORATE SOURCE: KRKA DD, Div Res & Dev, Dept Biochem Res & Drug Design, Cesta Brdo 49, Ljubljana 1000, Slovenia (Reprint)
AUTHOR: Brguljan P M; Krasovec M; Suskovic S; Kos J
CORPORATE SOURCE: KRKA DD, Div Res & Dev, Dept Biochem Res & Drug Design, Ljubljana 1000, Slovenia; Univ Clin Resp & Allerg Dis, Golnik, Slovenia; Jozef Stefan Inst, Dept Biochem & Mol Biol, Ljubljana, Slovenia
COUNTRY OF AUTHOR: Slovenia
SOURCE: PFLUGERS ARCHIV-EUROPEAN JOURNAL OF PHYSIOLOGY, (2001) Vol. 442, No. 6, Supp. [1], pp. R204-R206. ISSN: 0031-6768.
PUBLISHER: SPRINGER-VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 8
ENTRY DATE: Entered STN: 19 Oct 2001
Last Updated on STN: 19 Oct 2001

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cathepsin S (CS) has been proposed to be associated with asthma pathogenesis but its exact role is not established. In order to understand this proposed association our objective was to follow the 24-h concentration pattern of CS in sera from apparently healthy subjects and from steroid-independent and steroid-dependent asthmatics before and after one weeks' treatment with methylprednisolone (MP) and cyclosporin A (CsA), respectively. Blood samples were collected every 4 h over a 24-h period. Statistical evaluation of data for time effect was performed by one way ANOVA and least-squares fit of 24-h cosine. Little or no significant change of CS concentrations with time over a 24-h period was observed in healthy and asthmatic sera. CS concentrations were significantly lower in steroid-independent asthmatics compared to controls while there was no difference between healthy subjects and steroid-dependent asthmatics. After one week of therapy MP decreased CS concentrations while CsA had no effect. Our data suggest the involvement of CS in asthma pathogenesis and the potential use of CS levels as an additional biological parameter for monitoring the extent of disease and response to therapy.

L6 ANSWER 47 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:847093 SCISEARCH
THE GENUINE ARTICLE: 370NM

TITLE: Genetic association of a cystatin C gene polymorphism with late-onset Alzheimer disease

AUTHOR: Nitsch R M (Reprint)
CORPORATE SOURCE: Univ Zurich, Div Psychiat Res, August Forel Str 1, CH-8008 Zurich, Switzerland (Reprint)
AUTHOR: Finckh U; von der Kammer H; Velden J; Michel T; Andresen B; Deng A; Zhang J; Muller-Thomsen T; Zuchowski K; Menzer G; Mann U; Papassotiropoulos A; Heun R; Zurdel J; Holst F; Benussi L; Stoppe G; Reiss J; Miserez A R; Staehelin H B; Rebeck G W; Hyman B T; Binetti G; Hock C; Growdon J H
CORPORATE SOURCE: Univ Zurich, Div Psychiat Res, CH-8008 Zurich, Switzerland; Univ Hamburg, Hosp Eppendorf, Dept Human Genet, D-20246 Hamburg, Germany; Univ Hamburg, Hosp Eppendorf, Dept Psychiat, D-20246 Hamburg, Germany; Univ Hamburg, Ctr Mol Neurobiol, D-2000 Hamburg, Germany; Massachusetts Gen Hosp, Dept Neurol, Boston, MA 02114 USA; Univ Bonn, Dept Psychiat, D-5300 Bonn, Germany; Univ Goettingen, Dept Psychiat, Goettingen, Germany; Univ Goettingen, Dept Human Genet, Goettingen, Germany; Univ Basel, Basel, Switzerland; Sci Inst Res & Patient Care, Brescia, Italy
COUNTRY OF AUTHOR: Switzerland; Germany; USA; Italy
SOURCE: ARCHIVES OF NEUROLOGY, (NOV 2000) Vol. 57, No. 11, pp. 1579-1583.
ISSN: 0003-9942.
PUBLISHER: AMER MEDICAL ASSOC, 515 N STATE ST, CHICAGO, IL 60610 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 46
ENTRY DATE: Entered STN: 2000
Last Updated on STN: 2000
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective: To determine whether the cystatin C gene (CST3) is genetically associated with late-onset Alzheimer disease (AD).

Design: A case-control study with 2 independent study populations of patients with AD and age-matched, cognitively normal control subjects.

Setting: The Alzheimer's Disease Research Unit at the University Hospital Hamburg-Eppendorf, Hamburg, Germany, for the initial study (n=260). For the independent multicenter study (n=647), an international consortium that included the Massachusetts Alzheimer's Disease Research Center at the Massachusetts General Hospital, Boston; the Scientific Institute for Research and Patient Care, Brescia, Italy; and Alzheimer's research units at the Universities of Baseland Zurich, Switzerland, and Bonn, Goettingen, and Hamburg, Germany.

Participants: Five hundred seventeen patients with AD and 390 control subjects.

Measures: Molecular testing of the KspI polymorphisms in the 5' flanking region and exon 1 of CST3 and the apolipoprotein E (APOE) genotype. Mini-Mental State Examination scores for both patients with AD and control subjects.

Results: Homozygosity for haplotype B of CST3 was significantly associated with late-onset AD in both study populations, with an odds ratio of 3.8 (95% confidence interval, 1.56-9.25) in the combined data set; heterozygosity was not associated with an increased risk. The odds ratios for CST3 B/B increased from 2.6 in those younger than 75 years to 8.8 for those aged 75 years and older. The association of CST3 B/B with AD was independent of APOE epsilon4; both genotypes independently reduced disease-free survival.

Conclusions: CST3 is a susceptibility gene for late-onset AD, especially in patients aged 75 years and older. To our knowledge, CST3 B is the first autosomal recessive risk allele in late-onset AD.

L6 ANSWER 48 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:835253 SCISEARCH
THE GENUINE ARTICLE: 251WL
TITLE: Cystatin C deficiency in human atherosclerosis and aortic aneurysms
AUTHOR: Shi G P (Reprint)
CORPORATE SOURCE: Brigham & Womens Hosp, Div Resp, Dept Med, 75 Francis St, Boston, MA 02115 USA (Reprint)
AUTHOR: Sukhova G K; Grubb A; Ducharme A; Rhode L H; Lee R T; Ridker P M; Libby P; Chapman H A
CORPORATE SOURCE: Brigham & Womens Hosp, Div Resp, Dept Med, Boston, MA 02115 USA; Harvard Univ, Sch Med, Boston, MA 02115 USA; Univ Lund, Dept Clin Chem, Univ Hosp, S-22185 Lund, Sweden
COUNTRY OF AUTHOR: USA; Sweden
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (NOV 1999) Vol. 104, No. 9, pp. 1191-1197.
ISSN: 0021-9738.
PUBLISHER: AMER SOC CLINICAL INVESTIGATION INC, 35 RESEARCH DR, STE 300, ANN ARBOR, MI 48103 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 51
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The pathogenesis of atherosclerosis and abdominal aortic aneurysm involves breakdown of the elastic laminae. Elastolytic cysteine proteases, including cathepsins S and K, are overexpressed at sites of arterial elastin damage, but whether endogenous local inhibitors counterbalance these proteases is unknown. We show here that, whereas cystatin C is normally expressed in vascular wall smooth muscle cells (SMCs), this cysteine protease inhibitor is severely reduced in both atherosclerotic and aneurysmal aortic lesions. Furthermore, increased abdominal aortic diameter among 122 patients screened by ultrasonography correlated inversely with serum cystatin C levels. In vitro, cytokine-stimulated vascular SMCs secrete cathepsins, whose elastolytic activity could be blocked when cystatin C secretion was induced by treatment with TGF-beta(1). The findings highlight a potentially important role for imbalance between cysteine proteases and cystatin C in arterial wall remodeling and establish that cystatin C deficiency occurs in vascular disease.

L6 ANSWER 49 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:921776 SCISEARCH
THE GENUINE ARTICLE: YL445
TITLE: Interactions of proteases and protease inhibitors in Sertoli-germ cell cocultures preceding the formation of specialized Sertoli-germ cell junctions in vitro
AUTHOR: Mruk D (Reprint); Zhu L J; Silvestrini B; Lee W M; Cheng C Y
CORPORATE SOURCE: POPULAT COUNCIL, CTR BIOMED RES, NEW YORK, NY 10021; UNIV HONG KONG, DEPT ZOOL, HONG KONG, HONG KONG; UNIV ROMA LA SAPIENZA, INST PHARMACOL & PHARMACOGNOSY, ROME, ITALY
COUNTRY OF AUTHOR: USA; HONG KONG; ITALY
SOURCE: JOURNAL OF ANDROLOGY, (NOV-DEC 1997) Vol. 18, No. 6, pp. 612-622.
ISSN: 0196-3635.
PUBLISHER: AMER SOC ANDROLOGY, INC, C/O ALLEN PRESS, INC PO BOX 368,

LAWRENCE, KS 66044.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 72
ENTRY DATE: Entered STN: 1997
Last Updated on STN: 1997
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The biochemical mechanism(s) by which germ cells can form specialized junctions with Sertoli cells in the seminiferous epithelium at various stages of the spermatogenic cycle is unknown. This study sought to examine the biochemical changes that are involved when germ cells are cocultured with Sertoli cells in vitro preceding the establishment of specialized Sertoli-germ cell junctions. While isolated germ cells were allowed to attach to Sertoli cells, media from both the apical and basal compartments of bicameral units were collected to assess serine and cysteine protease activity, The expression of selected serine and cysteine proteases and their corresponding inhibitors in these Sertoli-germ cell cocultures was also examined by RT-PCR. Using an [I-125]-collagen film assay, a transient but significant increase in serine protease activity was noted in both the apical and basal compartments when germ cells began to settle onto the Sertoli cell monolayer preceding the formation of intercellular junctions, A specific tryptase (RNK-Tryp 2, a serine protease formerly cloned from a rat granular lymphocyte leukemia cell line, RNK-16, cDNA expression library) was shown to be expressed exclusively by Sertoli cells and not germ cells, Furthermore, Sertoli cell tryptase expression as well as urokinase plasminogen activator (u-PA, also a serine protease) increased significantly when germ cells were adhering to Sertoli cells. The decline in total serine protease activity when Sertoli-germ cell junctions were being formed was accompanied by a concomitant increase in alpha(2)-macroglobulin (alpha(2)-MG, a nonspecific protease inhibitor) expression. No significant changes in cysteine protease activity in either the apical or basal compartment were noted. However, there was a transient but significant increase in cathepsin L expression when germ cells were adhering to Serioli cells preceding cell junction formation. The subsequent reduction in cathepsin L expression after this transient increase was accompanied by a concomitant increase in cystatin C expression. These results suggest that proteases and their corresponding inhibitors are working synergistically and are likely to be involved in the adherence of germ cells to Sertoli cells and the subsequent formation of intercellular junctions.

L6 ANSWER 50 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1995:287795 SCISEARCH
THE GENUINE ARTICLE: QV930
TITLE: PERICELLULAR MOBILIZATION OF THE TISSUE-DESTRUCTIVE CYSTEINE PROTEINASES, CATHEPSIN-B, CATHEPSIN-L, AND CATHEPSIN-S, BY HUMAN MONOCYTE-DERIVED MACROPHAGES
AUTHOR: REDDY V Y (Reprint)
CORPORATE SOURCE: UNIV MICHIGAN, DEPT INTERNAL MED, ANN ARBOR, MI 48109 (Reprint)
AUTHOR: ZHANG Q Y; WEISS S J
CORPORATE SOURCE: UNIV MICHIGAN, CTR COMPREHENS CANC, ANN ARBOR, MI 48109
COUNTRY OF AUTHOR: USA
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (25 APR 1995) Vol. 92, No. 9, pp. 3849-3853.
ISSN: 0027-8424.
PUBLISHER: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 58
ENTRY DATE: Entered STN: 1995
Last Updated on STN: 1995
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Human macrophages are believed to damage host tissues in chronic inflammatory disease states, but these cells have been reported to express only modest degradative activity in vitro. However, while examining the ability of human monocytes to degrade the extracellular matrix component elastin, we identified culture conditions under which the cells matured into a macrophage population that displayed a degradative phenotype hundreds of times more destructive than that previously ascribed to any other cell population. The monocyte-derived macrophages synthesized elastinolytic matrix metalloproteinases (i.e., gelatinase B and matrilysin) as well as cysteine proteinases (i.e., cathepsins B, L, and S), but only the cathepsins were detected in the extracellular milieu as fully processed, mature enzymes by either vital fluorescence or active-site labeling. Consistent with these observations, macrophage-mediated elastinolytic activity was not affected by matrix metalloproteinase inhibitors but could be almost completely abrogated by inhibiting cathepsins L and S. These data demonstrate that human macrophages mobilize cysteine proteinases to arm themselves with a powerful effector mechanism that can participate in the pathophysiologic remodeling of the extracellular matrix.

L6 ANSWER 51 OF 78 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1994:222464 SCISEARCH
THE GENUINE ARTICLE: NF798
TITLE: DIFFERENTIAL DISTRIBUTION OF MESSENGER-RNAS FOR CATHEPSIN-B, CATHEPSIN-L AND CATHEPSIN-S IN ADULT-RAT BRAIN - AN IN-SITU HYBRIDIZATION STUDY
AUTHOR: PETANCESKA S (Reprint); BURKE S; WATSON S J; DEVI L
CORPORATE SOURCE: NYU, MED CTR, DEPT PHARMACOL, NEW YORK, NY 10016; UNIV MICHIGAN, MENTAL HLTH RES INST, ANN ARBOR, MI
COUNTRY OF AUTHOR: USA
SOURCE: NEUROSCIENCE, (APR 1994) Vol. 59, No. 3, pp. 729-738. ISSN: 0306-4522.
PUBLISHER: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 50
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The cysteine lysosomal proteases comprise a large family of highly conserved enzymes which are essential for intracellular protein turnover. These proteases are very efficient in their ability to degrade components of the extracellular matrix, and have been implicated in processes of cell growth, malignant transformation and inflammation. There is also a growing body of evidence for their involvement in the metabolism of the amyloid precursor protein. The production of insoluble beta A4 amyloid peptide is thought to be one of the key events that lead to the development of Alzheimer's pathology.

To see the physiological role these enzymes play in the brain, we studied the relative abundance and distribution of the messenger RNAs for three lysosomal cysteine proteases, cathepsins B and L and cathepsin S, by in situ hybridization histochemistry in

rat brain. All three enzymes are capable of degrading components of the extracellular matrix but they have different substrate preferences and resistances to neutral pH. We found that the mRNAs for cathepsins B, L, and S have different expression patterns in brain. Cathepsin B mRNA shows the highest level of expression. It has a wide distribution, and is preferentially expressed in neurons. The expression patterns of cathepsin B and cathepsin L mRNA overlap in many brain regions; in some areas they complement each other. Cathepsin B and L mRNAs are highly expressed in the choroid plexus, a structure that is instrumental in brain development. Both transcripts are also abundant in the neuropeptide synthesizing hypothalamic nuclei. Cathepsin S mRNA has wide expression pattern throughout brain, in grey and white matter. A great number of cells that express cathepsin S have microglial morphology.

Regions that are known to contain the highest amounts of the amyloid precursor protein express highest levels of cathepsin B and cathepsin L mRNA. Also, all three transcripts are highly represented in regions that are most prone to degeneration in Alzheimer's disease. These results suggest a role for these lysosomal hydrolases released from degenerating cells in the development of Alzheimer's pathology.

L6 ANSWER 52 OF 78 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER:	2008525009 EMBASE
TITLE:	Omics meets hypothesis-driven research: Partnership for innovative discoveries in vascular biology and angiogenesis.
AUTHOR:	Ruegg, Curzio (correspondence); Mariotti, Agnese
CORPORATE SOURCE:	Division of Experimental Oncology, Centre Pluridisciplinaire d'Oncologie, University of Lausanne, Epalinges, Switzerland. curzio.ruegg@unil.ch
AUTHOR:	Ruegg, Curzio (correspondence); Farmer, Pierre
CORPORATE SOURCE:	National Centre for Competence in Research (NCCR) Molecular Oncology, Epalinges, Switzerland. curzio.ruegg@unil.ch
AUTHOR:	Tissot, Jean-Daniel
CORPORATE SOURCE:	Service Regional Vaudois de Transfusion Sanguine, Lausanne, Switzerland.
AUTHOR:	Farmer, Pierre
CORPORATE SOURCE:	Swiss Institute of Bioinformatics, Bioinformatics Core Facility, Batiment Genopode, Lausanne, Switzerland.
AUTHOR:	Ruegg, Curzio (correspondence)
CORPORATE SOURCE:	Division of Experimental Oncology, Centre Pluridisciplinaire d'Oncologie, 155 Chemin des Boveresses, CH1066 Epalinges, Switzerland. curzio.ruegg@unil.ch
SOURCE:	Thrombosis and Haemostasis, (November 2008) Vol. 100, No. 5, pp. 738-746. Refs: 96 ISSN: 0340-6245 CODEN: THHADQ
PUBLISHER:	Schattauer GmbH, P.O. Box 104543, Stuttgart, D-70174, Germany.
COUNTRY:	Germany
DOCUMENT TYPE:	Journal; General Review; (Review)
FILE SEGMENT:	006 Internal Medicine 018 Cardiovascular Diseases and Cardiovascular Surgery 021 Developmental Biology and Teratology 022 Human Genetics 025 Hematology 029 Clinical and Experimental Biochemistry
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 10 Dec 2008 Last Updated on STN: 10 Dec 2008

AB The emergence of omics technologies allowing the global analysis of a given biological or molecular system, rather than the study of its individual components, has revolutionized biomedical research, including cardiovascular medicine research in the past decade. These developments raised the prospect that classical, hypothesis-driven, single gene-based approaches may soon become obsolete. The experience accumulated so far, however, indicates that omic technologies only represent tools similar to those classically used by scientists in the past and nowadays, to make hypothesis and build models, with the main difference that they generate large amounts of unbiased information. Thus, omics and classical hypothesis-driven research are rather complementary approaches with the potential to effectively synergize to boost research in many fields, including cardiovascular medicine. In this article we discuss some general aspects of omics approaches, and review contributions in three areas of vascular biology, thrombosis and haemostasis, atherosclerosis and angiogenesis, in which omics approaches have already been applied (vasculomics). .COPYRGT. 2008 Schattauer GmbH.

ACCESSION NUMBER: 2008405557 EMBASE

TITLE: Effect of statins on proteolytic activity in the wall of abdominal aortic aneurysms.

AUTHOR: Abisi, S.; Burnand, K.G.; Humphries, J.; Waltham, M.; Smith, A., Dr. (correspondence)
CORPORATE SOURCE: Academic Department of Surgery, Cardiovascular Division, King's College School of Medicine. alberto.smith@kcl.ac.uk
AUTHOR: Taylor, P.
CORPORATE SOURCE: Department of Surgery, Guy's and St Thomas'NHS Trust, St. Thomas' Hospital, London, United Kingdom.
AUTHOR: Smith, A., Dr. (correspondence)
CORPORATE SOURCE: Academic Department of Surgery, King's College School of Medicine, St Thomas' Hospital, London SE1 7EH, United Kingdom. alberto.smith@kcl.ac.uk

SOURCE: British Journal of Surgery, (March 2008) Vol. 95, No. 3, pp. 333-337.
Refs: 30
ISSN: 0007-1323 E-ISSN: 1365-2168 CODEN: BJSUAM
PUBLISHER: John Wiley and Sons Ltd, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom.
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Sep 2008
Last Updated on STN: 24 Sep 2008

AB Background: The aim of this study was to examine the effect of statin treatment on the activity of proteases in the wall of abdominal aortic aneurysms (AAAs). Methods: The activities of matrix metalloproteinases (MMPs) 9 and 3, cathepsins B, H, K, L and S, and the cystatin C level were measured in extracts of AAA wall taken from 82 patients undergoing AAA repair; 21 patients were receiving statin treatment before surgery. All values were standardized against soluble protein (SP) concentration in the extract, and reported as median (interquartile range) or mean(s.e.m.). Results: The two groups had similar demographics. Reduced activity of MMP-9 (43 (34-56) versus 80 (62-110) pg per mg SP; P < 0.001), cathepsin H (183 (117-366) versus 321 (172-644) nmol 4-methylcoumarin-7-amide released per mg SP; P = 0.016) and cathepsin L (102 (51-372) versus 287 (112-816) μmol

7-amino-4-trifluoromethylcoumarin released per mg SP; P = 0.020) was found in the statin-treated aortas compared with AAAs from patients not taking a statin. The statin-treated group had lower MMP-3 activity, but this did not reach statistical significance (P = 0.053). Cystatin C levels were higher in statin-treated aortas than in controls (41.3(3-1) versus 28.9(2.1) ng per mg SP; P = 0.003). Conclusion: Statins decreased the activity of proteases that have been implicated in aneurysm disease. Copyright .COPYRGT. 2008 British Journal of Surgery Society Ltd.

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ACCESSION NUMBER: 2007498664 EMBASE
TITLE: Cathepsin cysteine proteases in cardiovascular disease.
AUTHOR: Lutgens, Suzanne P. M.; Cleutjens, Kitty B. J. M.; Daemen, Mat J. A. P.; Heeneman, Sylvia (correspondence)
CORPORATE SOURCE: Department of Pathology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, P.O. Box 616, 6200 MD Maastricht, Netherlands. s.heeneman@path.unimaas.nl
SOURCE: FASEB Journal, (Oct 2007) Vol. 21, No. 12, pp. 3029-3041. Refs: 100
ISSN: 0892-6638 CODEN: FAJOEC
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jan 2008
Last Updated on STN: 31 Jan 2008

AB Extracellular matrix (ECM) remodeling is one of the underlying mechanisms in cardiovascular diseases. Cathepsin cysteine proteases have a central role in ECM remodeling and have been implicated in the development and progression of cardiovascular diseases. Cathepsins also show differential expression in various stages of atherosclerosis, and in vivo knockout studies revealed that deficiency of cathepsin K or S reduces atherosclerosis. Furthermore, cathepsins are involved in lipid metabolism. Cathepsins have the capability to degrade low-density lipoprotein and reduce cholesterol efflux from macrophages, aggravating foam cell formation. Although expression studies also demonstrated differential expression of cathepsins in cardiovascular diseases like aneurysm formation, neointima formation, and neovascularization, in vivo studies to define the exact role of cathepsins in these processes are lacking. Evaluation of the feasibility of cathepsins as a diagnostic tool revealed that serum levels of cathepsins L and S seem to be promising as biomarkers in the diagnosis of atherosclerosis, whereas cathepsin B shows potential as an imaging tool. Furthermore, cathepsin K and S inhibitors showed effectiveness in (pre) clinical evaluation for the treatment of osteoporosis and osteoarthritis, suggesting that cathepsin inhibitors may also have therapeutic effects for the treatment of atherosclerosis. .COPYRGT. FASEB.

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ACCESSION NUMBER: 2007432049 EMBASE
TITLE: Differential Expression of Cathepsins and Cystatin C in Ovine Uteroplacental Tissues.
AUTHOR: Song, G.; Bazer, F.W.; Spencer, T.E. (correspondence)
CORPORATE SOURCE: Center for Animal Biotechnology and Genomics, Department of Animal Science, Texas A and M University, 2471 TAMU, College Station, TX 77843-2471, United States. tspencer@tamu.edu

SOURCE: Placenta, (Oct 2007) Vol. 28, No. 10, pp. 1091-1098.
Refs: 34
ISSN: 0143-4004 CODEN: PLACDF
PUBLISHER IDENT.: S 0143-4004(07)00109-9
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 010 Obstetrics and Gynecology
021 Developmental Biology and Teratology
022 Human Genetics
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 9 Oct 2007
Last Updated on STN: 9 Oct 2007

AB Cathepsins (CTSs) are peptidases that have biological roles in degrading extracellular matrix, catabolism of intracellular proteins, and processing of pro-hormones. Cystatin C (CST3) is a secreted inhibitor of lysosomal cysteine proteases cathepsin B (CTSB) and CTSL. Our working hypothesis is that cathepsins and cystatins play important roles in implantation and placentation in sheep. Expression of CTSB, CTSD, CTSH, CTSK, CTSL, CTSS, CTSZ, and CST3 mRNAs was detected in ovine uteroplacental tissues with distinct temporal and/or spatial expression patterns between Days 40 and 120 of pregnancy. Of particular note, CTSB, CTSD, and CTSZ mRNAs were predominantly detected in the chorion of the placenta and were more abundant in the placentomes than the intercaruncular endometria. CTSL and CST3 mRNAs were abundant in the endometrial epithelia and chorion, whereas CTSK, CTSS and CTSH mRNAs were most abundant in the stratum compactum stroma of the intercaruncular endometrium. Consistent with localisation of mRNAs, immunoreactive CTSL and CST3 proteins were mainly observed in the intercaruncular endometrial glands and intercotyledonary placenta during later pregnancy. These results support the working hypothesis that CTS and CST3 in uteroplacental tissues are involved in endometrial remodelling and placentation in sheep. .COPYRGT. 2007 Elsevier Ltd. All rights reserved.

ACCESSION NUMBER: 2007356904 EMBASE
TITLE: Do cathepsins play a role in abdominal aortic aneurysm pathogenesis?.
AUTHOR: Sukhova, Galina K., Dr. (correspondence); Shi, Guo-Ping
CORPORATE SOURCE: Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA 02115, United States. gsukhova@rics.bwh.harvard.edu
SOURCE: Annals of the New York Academy of Sciences, (Nov 2006) Vol. 1085, pp. 161-169.
Editor: Tilson, David; Kuivaniemi, Helena; Upchurch, Gilbert, New York Academy of Sciences
Refs: 40
ISSN: 0077-8923 E-ISSN: 1749-6632 ISBN: 1573316571; 9781573316576 CODEN: ANYAA9
COUNTRY: United States
DOCUMENT TYPE: Book; Series; (Book Series); Conference Article; (Conference paper)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical and Experimental Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 9 Aug 2007
Last Updated on STN: 9 Aug 2007

AB Between 1998 and 1999 we suggested a role for cysteine proteases, particularly cathepsins S and K, in atherosclerosis and abdominal aortic aneurysm (AAA) formation. We also demonstrated the presence and activity of cathepsins S, K, and L in atherosclerotic and aneurysmal lesions in humans. Features unique to this family of extracellular enzymes indicate its likely participation in these vascular diseases. As very potent elastolytic enzymes, cathepsins are strong candidates as key participants in aneurysm development. Importantly, cathepsins express very high elastolytic activity in AAA due to reciprocal correlation with cystatin C, their most abundant endogenous inhibitor. Two opposite processes coexist in aneurysmal tissue: overexpression of elastolytic cathepsins, and severe suppression of cystatin C, probably due to differentially regulated expression and secretion of cathepsins and their inhibitors in response to inflammatory cytokines. Involvement of cathepsins in microvessel formation, a pathophysiological marker of human AAA, and programmed cell death (apoptosis), increases the likelihood of cathepsin participation in AAA formation and growth. We also summarize here results obtained in our and other laboratories that demonstrated reduced atherosclerosis and AAA in in vivo models using mice lacking different cathepsins. Deficiency of cysteine protease inhibitor cystatin C in atherosclerosis-prone ApoE-null mice leads to the development of specific features of AAA such as thinning of the tunica media and aortic dilatation. Taken together, such findings in humans in vitro with different cell types and in vivo in genetically altered mice demonstrate the importance of cysteine protease/protease inhibitor balance in dysregulated arterial integrity and remodeling during atherosclerosis and aortic aneurysm formation. .COPYRGT. 2006 New York Academy of Sciences.

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ACCESSION NUMBER:	2006599352 EMBASE
TITLE:	Cysteine cathepsins: Regulators of antitumour immune response.
AUTHOR:	Kos, Janko (correspondence)
CORPORATE SOURCE:	University of Ljubljana, Department of Pharmaceutical Biology, Faculty of Pharmacy, Askerceva 7, SI-1000 Ljubljana, Slovenia. Janko.kos@ffa.uni-lj.si
AUTHOR:	Obermajer, Natasa; Doljak, Bojan
SOURCE:	Expert Opinion on Biological Therapy, (Dec 2006) Vol. 6, No. 12, pp. 1295-1309. Refs: 120 ISSN: 1471-2598 CODEN: EOBTA2
COUNTRY:	United Kingdom
DOCUMENT TYPE:	Journal; General Review; (Review)
FILE SEGMENT:	016 Cancer 026 Immunology, Serology and Transplantation 029 Clinical and Experimental Biochemistry
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 12 Jan 2007 Last Updated on STN: 12 Jan 2007

AB Cysteine cathepsins are lysosomal cysteine proteases that are involved in a number of important biological processes, including intracellular protein turnover, propeptide and hormone processing, apoptosis, bone remodelling and reproduction. In cancer, the cathepsins have been linked to extracellular matrix remodelling and to the promotion of tumour cell motility, invasion, angiogenesis and metastasis, resulting in poor outcome of cancer patients; however, cysteine cathepsins are also involved at different levels of the innate and adaptive immune responses. Their best known role in this aspect is their contribution to major histocompatibility complex class II antigen presentation, the processing

of progranzymes into proteolytically active forms, cytotoxic lymphocyte self-protection, cytokine and growth factor degradation and, finally, the induction of cytokine expression and modulation of integrin function. This review is focused on the role of cysteine cathepsins in the antitumour immune response and the evaluation of their pro- and anticancer behaviours during the regulation of these processes. .COPYRGT. 2006 Informa UK Ltd.

L6 ANSWER 58 OF 78 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2006516598 EMBASE
TITLE: Serum cystatin C as a marker of glomerular filtration rate.
AUTHOR: Madero, Magdalena; Sarnak, Mark J.; Stevens, Lesley A., Dr. (correspondence)
CORPORATE SOURCE: Division of Nephrology, Tufts-New England Medical Center, Boston, MA, United States. lstevens1@tufts-nemc.org
AUTHOR: Stevens, Lesley A., Dr. (correspondence)
CORPORATE SOURCE: Box 391, 750 Washington St, Boston, MA 02111, United States. lstevens1@tufts-nemc.org
SOURCE: Current Opinion in Nephrology and Hypertension, (Nov 2006) Vol. 15, No. 6, pp. 610-616.
Refs: 48
ISSN: 1062-4821 CODEN: CNHYEM
PUBLISHER IDENT.: 00041552200611100000011
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 028 Urology and Nephrology
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 9 Nov 2006
Last Updated on STN: 9 Nov 2006
AB PURPOSE OF REVIEW: Glomerular filtration rate is widely accepted as the best overall measure of kidney function. Currently available methods to estimate glomerular filtration rate have strengths and limitations. Cystatin C is a novel endogenous filtration marker being considered as a potential replacement for serum creatinine. This review summarizes the currently available glomerular filtration rate estimating equations based on cystatin C and the literature comparing cystatin C and creatinine as filtration markers. RECENT FINDINGS: In most cystatin C estimating equations, inclusion of age and sex did not substantially improve their performance. Equations yield different glomerular filtration rate estimates for the same level of cystatin C. Variation among equations may be due to differences among the assays or populations in the individual studies. Studies comparing cystatin C with creatinine or creatinine-based estimating equations show heterogeneous results, with some showing improved performance and others showing equivalent performance even in similar populations. These heterogeneous results may be due to inappropriate comparisons between equations developed in one population with those developed in another, or to the differences between assays or population characteristics. SUMMARY: Cystatin C shows promise as an alternative to serum creatinine but several important questions remain before it can be recommended for use in clinical practice. .COPYRGT. 2006 Lippincott Williams & Wilkins, Inc.

L6 ANSWER 59 OF 78 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2006471802 EMBASE
TITLE: Cysteine cathepsins: Multifunctional enzymes in cancer.

AUTHOR: Mohamed, Mona Mostafa; Sloane, Bonnie F. (correspondence)
CORPORATE SOURCE: Department of Pharmacology, Wayne State University School of Medicine, Detroit, MI 48201, United States. bsloane@med.wayne.edu
AUTHOR: Mohamed, Mona Mostafa
CORPORATE SOURCE: Department of Zoology, Faculty of Science, Cairo University, Egypt.
AUTHOR: Sloane, Bonnie F. (correspondence)
CORPORATE SOURCE: Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, United States. bsloane@med.wayne.edu
SOURCE: Nature Reviews Cancer, (Oct 2006) Vol. 6, No. 10, pp. 764-775.
Refs: 145
ISSN: 1474-175X CODEN: NRCAC4
PUBLISHER IDENT.: NRC1949
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 016 Cancer
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Oct 2006
Last Updated on STN: 16 Oct 2006

AB Cysteine cathepsins are highly upregulated in a wide variety of cancers by mechanisms ranging from gene amplification to post-transcriptional modification. Their localization within intracellular lysosomes often changes during neoplastic progression, resulting in secretion of both inactive and active forms and association with binding partners on the tumour cell surface. Secreted, cell-surface and intracellular cysteine cathepsins function in proteolytic pathways that increase neoplastic progression. Direct proof for causal roles in tumour growth, migration, invasion, angiogenesis and metastasis has been shown by downregulating or ablating the expression of individual cysteine cathepsins in tumour cells and in transgenic mouse models of human cancer. .COPYRGT. 2006 Nature Publishing Group.

L6 ANSWER 60 OF 78 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2006345822 EMBASE
TITLE: Caenorhabditis elegans: Study model for animal and human cathepsins and inhibitors.
AUTHOR: Hashmi, Sarwar (correspondence)
CORPORATE SOURCE: Laboratory of Molecular Parasitology, Lindsley F. Kimball Research Institute, New York Blood Center, 310 East 67th Street, New York, NY 10021, United States. shashmi@nybloodcenter.org
AUTHOR: Anwer, Khursheed
CORPORATE SOURCE: Expression Genetics Inc., 2215 Mock Road, Huntsville, AL 35801, United States.
AUTHOR: Bilgrami, Anwar L.
CORPORATE SOURCE: Department of Entomology, Rutgers University, 93 Lipman Drive, Blake Hall, New Brunswick, NJ 08901, United States.
AUTHOR: Hashmi, Sarwar (correspondence)
CORPORATE SOURCE: Laboratory of Molecular Parasitology, Lindsley F. Kimbal Research Institute, New York Blood Center, 310 East 67th Street, New York, NY 10021, United States. shashmi@nybloodcenter.org
SOURCE: Current Enzyme Inhibition, (May 2006) Vol. 2, No. 2, pp. 173-188.
Refs: 236
ISSN: 1573-4080

COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
004 Microbiology: Bacteriology, Mycology, Parasitology and Virology
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 8 Aug 2006
Last Updated on STN: 8 Aug 2006

AB Cysteine proteases belong to C1 family, which includes plant and lysosomal cathepsin-like proteases. Cathepsins, detected and isolated from numerous biological sources, are well adapted to acidic and reducing conditions of lysosomal system. Cathepsins perform the activities of a wide variety of enzymes such as broad- and narrow-range endo-peptidases, aminopeptidases, dipeptidyl peptidases with exo- and endopeptidases. They are involved in many physiological events. The enzymes can be destructive if their activity is not controlled by their endogenous inhibitors. Eleven cathepsins, i.e., B, C, F, H, K, L, O, S, V, W, and X or Z, designated so far in human are also identified in other organisms. Although there are great deal of information available on the physiological function of these cathepsins at cellular level very little is known about their function at organism level. The genome sequences from many organisms including human, Drosophila, and free-living nematode, Caenorhabditis elegans allow comparative genomics as the first order functional analysis. The genome sequence of C. elegans allows comparative sequence analyses to identify parasite or human gene that share homology with C. elegans. Genome sequences in combination with an ideal model system such as C. elegans will facilitate identification of key cellular functions that could lead to the identification of mechanisms of drug resistance, as well as discovery of novel drug targets and antigens with vaccine potential. This review covers recent research on the role of "papain-like" class of cysteine proteases in cellular physiology and focuses on most comprehensively studied cathepsin B and L enzymes in C. elegans. Besides, it also reviews the function of a recently described cathepsin Z. .COPYRGT. 2006 Bentham Science Publishers Ltd.

ACCESSION NUMBER: 2006234444 EMBASE
TITLE: Comprehensive transcriptome of proteases and protease inhibitors in vascular cells.
AUTHOR: Shi, Guo-Ping, Dr. (correspondence)
CORPORATE SOURCE: Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States. gshi@rics.bwh.harvard.edu
AUTHOR: Dolganov, Gregory M.
CORPORATE SOURCE: Department of Medicine, University of California, San Francisco, CA, United States.
AUTHOR: Shi, Guo-Ping, Dr. (correspondence)
CORPORATE SOURCE: Cardiovascular Medicine, NRB-7, 77 Avenue Louis Pasteur, Boston, MA 02115, United States. gshi@rics.bwh.harvard.edu
SOURCE: Stroke, (Feb 2006) Vol. 37, No. 2, pp. 537-541.
Refs: 8
ISSN: 0039-2499 CODEN: SJCCA7
PUBLISHER IDENT.: 00007670200602000000084
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy

008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 8 Jun 2006
Last Updated on STN: 8 Jun 2006

AB Background and Purpose - Smooth muscle cells, endothelial cells, and macrophages are essential components of the vasculature, of which the homeostatic gene expression participate importantly in the maintenance of vascular wall integrity. The pathogenesis of vascular diseases, such as cerebral ischemia, atherosclerosis, and abdominal aortic aneurysms, often associates with inflammation and altered gene expression, including proteolytic enzymes that play multiple and important roles in extracellular matrix degradation, cell proliferation and migration, and latent enzyme or growth factor activation. Methods and Results - Human saphenous vein smooth muscle cells, endothelial cells, and monocyte-derived macrophages from 3 independent donors were stimulated with interleukin 1β, interferon γ, tumor necrosis factor α, basic fibroblast growth factor, and vascular endothelial growth factor, 5 common proinflammatory mediators often found in diseased human microvessels and macrovessels. Quantitative real-time PCR was used to examine the mRNA levels of 49 proteolytic enzymes and their inhibitors, selected from 4 protease families, in these vascular cells. Conclusions - Although primary cultured cells from different donors may behave differently in response to these proinflammatory cytokines, data from this study revealed a broad view of vascular cell protease expression profiles under inflammatory conditions, critical to studies of inflammation-associated vascular tissue remodeling. .COPYRGT. 2006 American Heart Association, Inc.

ACCESSION NUMBER: 2006072910 EMBASE
TITLE: Imbalance between cysteine proteases and inhibitors in a baboon model of bronchopulmonary dysplasia.
AUTHOR: Cataltepe, Sule, Dr. (correspondence)
CORPORATE SOURCE: Division of Newborn Medicine, Children's Hospital, Enders 950, 300 Longwood Avenue, Boston, MA 02115, United States. sule.cataltepe@childrens.harvard.edu
AUTHOR: Altiok, Ozden; Yasumatsu, Ryuji; Bingol-Karakoc, Gulbin; Riese, Richard J.; Stahlman, Mildred T.; Dwyer, William; Pierce, Richard A.; Bromme, Dieter; Weber, Ekkehard
SOURCE: American Journal of Respiratory and Critical Care Medicine, (1 Feb 2006) Vol. 173, No. 3, pp. 318-326.
Refs: 56
ISSN: 1073-449X E-ISSN: 1073-449X CODEN: AJCMED
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 2006
Last Updated on STN: 3 Mar 2006

AB Rationale: Bronchopulmonary dysplasia (BPD) continues to be a major morbidity in preterm infants. The lung pathology in BPD is characterized by impaired alveolar and capillary development. An imbalance between proteases and protease inhibitors in association with changes in lung elastic fibers has been implicated in the pathogenesis of BPD. Objective: To investigate the expression and activity levels of papain-like lysosomal cysteine proteases, cathepsins B, H, K, L, S, and their inhibitors, cystatins B and C, in a baboon model of BPD. Methods: Real-time reverse transcriptase-polymerase chain reaction, immunohistochemistry,

immunoblotting, active site labeling of cysteine proteases, and in situ hybridization were performed. Measurements and Main Results: The steady-state mRNA and protein levels of all cathepsins were significantly increased in the lung tissue of baboons with BPD. In contrast, the steady-state mRNA and protein levels of two major cysteine protease inhibitors, cystatin B and C, were unchanged. Correlating with these alterations, the activity of cysteine proteases in lung tissue homogenates and bronchoalveolar lavage fluid was significantly higher in the BPD group. The levels of cathepsin B, H, and S increased and cathepsin K decreased with advancing gestation. All cathepsins, except for cat K, were immunolocalized to macrophages in BPD. In addition, cathepsin H and cystatin B were colocalized in type 2 alveolar epithelial cells. Cathepsin L was detected in some bronchial epithelial, endothelial, and interstitial cells. Cathepsin K was localized to some perivascular cells by in situ hybridization. Conclusions: Cumulatively, these findings demonstrate an imbalance between cysteine proteases and their inhibitors in BPD.

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ACCESSION NUMBER: 2006018679 EMBASE
TITLE: Active cathepsins B, H, K, L and S in human inflammatory bronchoalveolar lavage fluids.
AUTHOR: Serveau-Avesque, Carole; Ferrer-Di Martino, Michele; Herve-Grepinet, Virginie; Hazouard, Eric; Gauthier, Francis; Diot, Elisabeth; Lalmanach, Gilles (correspondence)
CORPORATE SOURCE: INSERM U618, F-37000 Tours Cedex, France. gilles.lalmanach@univ-tours.fr
AUTHOR: Serveau-Avesque, Carole; Ferrer-Di Martino, Michele; Herve-Grepinet, Virginie; Hazouard, Eric; Gauthier, Francis; Diot, Elisabeth; Lalmanach, Gilles (correspondence)
CORPORATE SOURCE: Universite Francois Rabelais, F-37000 Tours Cedex, France. gilles.lalmanach@univ-tours.fr
AUTHOR: Serveau-Avesque, Carole; Ferrer-Di Martino, Michele; Herve-Grepinet, Virginie; Hazouard, Eric; Gauthier, Francis; Diot, Elisabeth; Lalmanach, Gilles (correspondence)
CORPORATE SOURCE: IRF 135, F-37000 Tours Cedex, France. gilles.lalmanach@univ-tours.fr
AUTHOR: Serveau-Avesque, Carole
CORPORATE SOURCE: INSERM U476, Nutrition Humaine et Lipides: Biodisponibilite, Metabolisme et Regulations, Faculte de Medecine de la Timone, F-13385 Marseille Cedex 05, France.
AUTHOR: Lalmanach, Gilles (correspondence)
CORPORATE SOURCE: INSERM U618, Proteases et Vectorisation Pulmonaires, Universite Francois Rabelais, 10 Bd Tonnelle, F-37032 Tours Cedex, France. gilles.lalmanach@univ-tours.fr
SOURCE: Biology of the Cell, (Jan 2006) Vol. 98, No. 1, pp. 15-22. Refs: 50
ISSN: 0248-4900 CODEN: BCELDF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 Jan 2006
Last Updated on STN: 26 Jan 2006

AB Background information. Chronic inflammation and tissue remodelling result from an imbalance between proteolytic enzymes and their inhibitors

in the lungs in favour of proteolysis. While many studies have examined serine proteases (e.g. cathepsin G and neutrophil elastase) and matrix metalloproteases, little is known about the role of papain-like CPs (cysteine proteases). The present study focuses on the thiol-dependent cathepsins (CPs) and their specific cystatin-like inhibitors [CPIs (CP inhibitors)] in human inflammatory BALFs (BAL fluids, where BAL stands for broncho-alveolar lavage). Results. Cathepsins B, K and S found were mostly zymogens, whereas cathepsins H and L were predominantly in their mature forms. Little immunoreactive cystatin C was found and the high- and low-molecular-mass ('weight') kininogens were extensively degraded. The BALF procathepsins B and L could be activated autocatalytically, indicating that alveolar fluid pro-CPs are reservoirs of mature enzymes. Hydrolysis patterns of 7-amino-4-methylcoumarin-derived peptide substrates showed that extracellular alveolar CPs remain proteolytically active, and that cathepsins B and L are the most abundant thiol-dependent endoproteases. The CP/CPI balance was significantly tipped in favour of cathepsins (3- or 5-fold), as confirmed by the extensive CP-dependent degradation of exogenous kininogens by BALFs. Conclusions. Although their importance for inflammation remains to be clarified, the presence of active cathepsins L, K and S suggests that they contribute to the extracellular breakdown of the extracellular matrix. .COPYRGT. Portland Press 2006.

ACCESSION NUMBER: 2005198390 EMBASE
TITLE: The human brain mannose 6-phosphate glycoproteome: A complex mixture composed of multiple isoforms of many soluble lysosomal proteins.
AUTHOR: Sleat, David E.; Lackland, Henry; Wang, Yanhong; Sohar, Istvan; Xiao, Gang; Lobel, Peter, Dr. (correspondence)
CORPORATE SOURCE: Ctr. for Adv. Biotech. and Medicine, Univ. of Med./Dent. of New Jersey, Piscataway, NJ, United States. sleat@cabm.rutgers.edu; lobel@cabm.rutgers.edu
AUTHOR: Sleat, David E.; Lobel, Peter, Dr. (correspondence)
CORPORATE SOURCE: Department of Pharmacology, Univ. of Med./Dent. of New Jersey, Piscataway, NJ, United States. sleat@cabm.rutgers.edu; lobel@cabm.rutgers.edu
AUTHOR: Li, Hong
CORPORATE SOURCE: Dept. of Biochem. and Molec. Biology, New Jersey Medical School, Newark, NJ, United States.
AUTHOR: Lobel, Peter, Dr. (correspondence)
CORPORATE SOURCE: Ctr. for Adv. Biotech. and Medicine, 679 Hoes Lane, Piscataway, NJ 08854, United States. lobel@cabm.rutgers.edu
AUTHOR: Xiao, Gang
CORPORATE SOURCE: Genomics Institute, University of Pennsylvania, Philadelphia, PA 10104, United States.
SOURCE: Proteomics, (Apr 2005) Vol. 5, No. 6, pp. 1520-1532.
Refs: 41
ISSN: 1615-9853 CODEN: PROTC7
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 May 2005
Last Updated on STN: 26 May 2005

AB The lysosome is a membrane delimited cytoplasmic organelle that contains at least 50 hydrolytic enzymes and associated cofactors. The biomedical importance of these enzymes is highlighted by the many lysosomal storage disorders that are associated with mutations in genes encoding lysosomal proteins, and there is also evidence that lysosomal activities may be

involved in more widespread human diseases. The aim of this study was to characterize the human brain lysosomal proteome with the goal of establishing a reference map to investigate human diseases of unknown etiology and to gain insights into the cellular function of the lysosome. Proteins containing mannose 6-phosphate (Man6-P), a carbohydrate modification used for targeting resident soluble lysosomal proteins to the lysosome, were affinity-purified using immobilized Man6-P receptor. Fractionation by two-dimensional electrophoresis resolved a complex mixture comprising approximately 800 spots. Constituent proteins in each spot were identified using a combination of matrix-assisted laser desorption/ionization- time of flight mass spectrometry (both mass spectrometry (MS/MS) and tandem peptide mass fingerprinting) on in-gel tryptic digests and N-terminal sequencing. In a complementary analysis, we also analyzed a tryptic digest of the unfractionated mixture by liquid chromatography MS/MS. In total, 61 different proteins were identified. Seven were likely contaminants associated with true Man6-P glycoproteins. Forty-one were known lysosomal proteins of which 11 have not previously been reported to contain Man6-P. An additional nine proteins were either uncharacterized or proteins not previously reported to have lysosomal function. We found that the human brain Man6-P-containing lysosomal proteome is highly complex and contains more proteins with a much greater number of individual isoforms than found in previous studies of Man6-P glycoproteomes. .COPYRGT. 2005 WILEY-VCH Verlag GmbH & Co. KGaA.

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ACCESSION NUMBER: 2004521855 EMBASE
TITLE: Cysteine cathepsins in human cancer.
AUTHOR: Jedeszko, Christopher; Sloane, Bonnie F. (correspondence)
CORPORATE SOURCE: Department of Pharmacology, Wayne State University, Detroit, MI 48201, United States. bsloane@med.wayne.edu
AUTHOR: Sloane, Bonnie F. (correspondence)
CORPORATE SOURCE: Barbara Ann Karmanos Cancer Inst., Wayne State University, Detroit, MI 48201, United States. bsloane@med.wayne.edu
SOURCE: Biological Chemistry, (Nov 2004) Vol. 385, No. 11, pp. 1017-1027.
Refs: 124
ISSN: 1431-6730 CODEN: BICHF3
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 28 Dec 2004
Last Updated on STN: 28 Dec 2004

AB Proteases play causal roles in the malignant progression of human tumors. This review centers on the roles in this process of cysteine cathepsins, i.e., peptidases belonging to the papain family (C1) of the CA clan of cysteine proteases. Cysteine cathepsins, most likely along with matrix metalloproteases (MMPs) and serine proteases, degrade the extracellular matrix, thereby facilitating growth and invasion into surrounding tissue and vasculature. Studies on tumor tissues and cell lines have shown changes in expression, activity and distribution of cysteine cathepsins in numerous human cancers. Molecular, immunologic and pharmacological strategies to modulate expression and activity of cysteine cathepsins have provided evidence for a causal role for these enzymes in tumor progression and invasion. Clinically, the levels, activities and localization of cysteine cathepsins and their endogenous inhibitors have been shown to be

of diagnostic and prognostic value. Understanding the roles that cysteine proteases play in cancer could lead to the development of more efficacious therapies. Copyright .COPYRGT. by Walter de Gruyter.

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ACCESSION NUMBER: 2004454110 EMBASE
TITLE: Serum cystatin C in patients with hemoblastosis.
AUTHOR: Usova, T.A. (correspondence); Korolenko, T.A.
CORPORATE SOURCE: Institute of Physiology, Russian Academy of Medical Sciences, ul. Timakova 4, 630117 Novosibirsk, Russian Federation. T.A.Korolenko@iph.ma.nsc.ru
AUTHOR: Poteryaeva, O.N.
CORPORATE SOURCE: Institute of Biochemistry, Russian Academy of Medical Sciences, ul. Timakova 4, 630117 Novosibirsk, Russian Federation.
AUTHOR: Pospelova, T.I.
CORPORATE SOURCE: Novosibirsk Medical Academy, Novosibirsk, Russian Federation.
AUTHOR: Usova, T.A. (correspondence)
CORPORATE SOURCE: Laboratory of Cellular Biochemistry, Institute of Physiology, Russian Academy of Medical Sciences, ul. Tomakova 4, 630117 Novosibirsk, Russian Federation.
SOURCE: International Journal of Immunotherapy, (2003) Vol. 19, No. 2-4, pp. 61-65.
Refs: 17
ISSN: 0255-9625 CODEN: IJIMET
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Nov 2004
Last Updated on STN: 12 Nov 2004

AB Human cystatin C is a natural inhibitor of cysteine proteinases involved in the regulation of activity of endogenous cysteine proteinases (cathepsins B, L, H, S) and extracellular control of cysteine proteinase activities. During tumor progression, human cystatin C plays a role in penetration of normal tissues by malignant cells, and inverse correlation between cystatin C and malignant progression has been shown. Serum cystatin C concentration was measured in patients with hemoblastosis. We observed increasing serum cystatin C concentration in patients with non-Hodgkin's lymphoma, Hodgkin's lymphoma and multiple myeloma, which partially returned to normal levels after courses of antitumor treatment. .COPYRGT. 2003 Bioscience Ediprint Inc.

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ACCESSION NUMBER: 2004416443 EMBASE
TITLE: Cysteine protease cathepsin S as a key step in antigen presentation.
AUTHOR: Liu, Weimin
CORPORATE SOURCE: Department of Medicinal Chemistry, B. Ingelheim Pharmaceuticals, Inc..
AUTHOR: Spero, Denice M., Dr. (correspondence)

CORPORATE SOURCE: Department of Drug Discovery Support, B. Ingelheim Pharmaceuticals, Inc.. dspero@rdg.boehringer-ingelheim.com
AUTHOR: Spero, Denice M., Dr. (correspondence)
CORPORATE SOURCE: R and D 6-5, P.O. Box 368, Ridgefield, CT 06877, United States. dspero@rdg.boehringer-ingelheim.com
SOURCE: Drug News and Perspectives, (Jul 2004) Vol. 17, No. 6, pp. 357-363.
Refs: 83
ISSN: 0214-0934 CODEN: DNPEED
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Oct 2004
Last Updated on STN: 18 Oct 2004

AB Cathepsin S is a cysteine protease in the papain super-family. Studies have shown that it is highly expressed in antigen-presenting cells. Along with other lysosomal proteases, cathepsin S plays an important role in the major histocompatibility complex class II-restricted antigen presentation, especially in the degradation of the invariant chain, a chaperone peptide bound to the class II complex. Compared with other lysosomal cysteine proteases, cathepsin S has displayed some unique characteristics. As a result, cathepsin S has been implicated as a potential target in the treatment of various disorders ranging from autoimmune diseases to atherosclerosis. Furthermore, a number of small-molecule cathepsin S inhibitors have demonstrated efficacy in disease-relevant models. .COPYRGT. 2004 Prous Science.

L6 ANSWER 68 OF 78 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004224040 EMBASE
TITLE: Up regulation of cathepsin K expression in articular chondrocytes in a transgenic mouse model for osteoarthritis.
AUTHOR: Vuorio, E.I., Dr. (correspondence)
CORPORATE SOURCE: Dept. Med. Biochem. and Molec. Biol., University of Turku, FIN-20520 Turku, Finland. eero.vuorio@utu.fi
AUTHOR: Morko, J.P.; Soderstrom, M.; Saamanen, A.-M.K.; Salminen, H.J.; Vuorio, E.I., Dr. (correspondence)
CORPORATE SOURCE: Skeletal Research Programme, Dept. of Med. Biochem. Molec. Biol., University of Turku, FIN-20520 Turku, Finland. eero.vuorio@utu.fi
SOURCE: Annals of the Rheumatic Diseases, (Jun 2004) Vol. 63, No. 6, pp. 649-655.
Refs: 51
ISSN: 0003-4967 CODEN: ARDIAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
031 Arthritis and Rheumatism
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jul 2004
Last Updated on STN: 9 Jul 2004

AB Objectives: To study the expression of cysteine proteinases, particularly cathepsin K, and their extracellular inhibitor cystatin

C in articular cartilage of transgenic Del1 mice which harbour a short deletion mutation in a type II collagen transgene and are predisposed to early onset osteoarthritis. Methods: Northern analysis was used to measure mRNA levels of cathepsins B, H, K, L, and S, and cystatin C in total RNA extracted from knee joints of Del1 mice, using their non-transgenic litter mates as controls. Immunohistochemistry and morphometry was used to study the distribution of cathepsin K and cystatin C in the knee joints. Results: Up regulation of cathepsin K mRNA expression was seen in the knee joints of transgenic Del1 mice at the onset of cartilage degeneration. Cathepsin K was found near sites of matrix destruction in articular chondrocytes, particularly in clusters of proliferating cells, and in calcified cartilaginous matrix. In intact articular cartilage of control animals, cathepsin K was only seen in a small number of chondrocytes. Upon aging, control animals also developed osteoarthritis, which was accompanied by increased cathepsin K expression. Cystatin C was mostly localised in and around chondrocytes located in calcified cartilage, with no obvious association with the onset of cartilage degeneration. Conclusion: The temporospatial distribution of cathepsin K in osteoarthritic cartilage suggests a role for this enzyme in the pathogenesis of osteoarthritis. Because cathepsin K can digest cartilage matrix components it may contribute to the development of osteoarthritic lesions. These data may provide new clues for the development of treatments aimed at preventing cartilage degeneration.

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ACCESSION NUMBER: 2003510729 EMBASE
TITLE: Probing Dendritic Cell Function by Guiding the Differentiation of Embryonic Stem Cells.
AUTHOR: Fairchild, Paul J. (correspondence); Nolan, Kathleen F.; Waldmann, Herman
CORPORATE SOURCE: Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford, OX1 3RE, United Kingdom.
SOURCE: Methods in Enzymology, (2003) Vol. 365, pp. 169-186. Refs: 29
ISSN: 0076-6879 CODEN: MENZAU
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jan 2004
Last Updated on STN: 16 Jan 2004

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ACCESSION NUMBER: 2003374083 EMBASE
TITLE: Novel cell-permeable acyloxymethylketone inhibitors of asparaginyl endopeptidase.
AUTHOR: Loak, Kylie; Billson, Jeremy; Morton, Fraser; Hewitt, Ellen
CORPORATE SOURCE: Medivir UK Ltd., 100 Fulbourn Road, Cambridge CB1 9PT, United Kingdom.
AUTHOR: Li, Dongtao Ni; Manoury, Benedicte; Watts, Colin (correspondence)
CORPORATE SOURCE: Division of Cell Biology/Immunology, School of Life Science, University of Dundee, Dundee DD1 4HN, United Kingdom.
SOURCE: Biological Chemistry, (1 Aug 2003) Vol. 384, No. 8, pp. 1239-1246. Refs: 25

ISSN: 1431-6730 CODEN: BICHF3
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 2003
Last Updated on STN: 2 Oct 2003

AB Mammalian asparaginyl endopeptidase (AEP) or legumain is a recently identified lysosomal cysteine protease belonging to clan CD. To date it has been shown to be involved in antigen presentation within class II MHC positive cells and in pro-protein processing. Further elucidation of the biological functions of the enzyme will require potent and selective inhibitors and thus we describe here new acyloxymethylketone inhibitors of AEP. The most potent of the series is 2,6-dimethyl-benzoic acid 3-benzyloxycarbonylamino-4-carbamoyl-2-oxo-butyl ester (MV026630) with a k(obs)/[I] value of 1.09x10(5) M(-1)s(-1). At low μm concentrations this compound is able to enter living cells and irreversibly inactivate AEP. We show that this results in inhibition of AEP autoactivation and in perturbation of the processing and presentation of T cell epitopes from both tetanus toxin and myelin basic protein.

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ACCESSION NUMBER: 2003008823 EMBASE
TITLE: Inflammatory stimuli recruit cathepsin activity to late endosomal compartments in human dendritic cells.
AUTHOR: Lautwein, Alfred; Burster, Timo; Kalbacher, Hubert; Driessen, Christoph
CORPORATE SOURCE: Med. Natural Sci./Research Center, University of Tubingen, Tubingen, Germany. christoph.driessen@uni-tuebingen.de
AUTHOR: Lennon-Dumenil, Ana-Marie
CORPORATE SOURCE: Department of Pathology, Harvard Medical School, Boston, United States.
AUTHOR: Overkleeft, Herman S.
CORPORATE SOURCE: Leiden Institute of Chemistry, Gorleaus Laboratory, Leiden, Netherlands.
AUTHOR: Weber, Ekkehard
CORPORATE SOURCE: Institute of Physiological Chemistry, University of Halle, Halle, Germany.
AUTHOR: Lautwein, Alfred; Burster, Timo; Driessen, Christoph
CORPORATE SOURCE: Department of Medicine II, University of Tubingen, Tubingen, Germany. christoph.driessen@uni-tuebingen.de
AUTHOR: Driessen, C.C. (correspondence)
CORPORATE SOURCE: MNF Universitat Tubingen, Ob dem Himmelreich 7, 72074 Tubingen, Germany. christoh.driessen@uni-tuebingen.de
SOURCE: European Journal of Immunology, (1 Dec 2002) Vol. 32, No. 12, pp. 3348-3357.
Refs: 30
ISSN: 0014-2980 CODEN: EJIMAF
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jan 2003
Last Updated on STN: 16 Jan 2003

AB Proteolysis by endocytic cysteine proteases is a central element of the antigen-presentation machinery in dendritic cells (DC). It controls the

generation of immunogenic peptides, guides the transit of both MHC class II and MHC-like molecules through the endocytic compartment and converts class II into a peptide-receptive state - features closely linked to DC maturation. Differential activity of endocytic proteases, in particular cathepsins, in subcellular compartments has been implicated as a key regulatory element in controlling this machinery in murine DC. We analyzed the expression and subcellular distribution of the major endocytic cysteine proteases (cathepsins S, B, L and H) along with their major endogenous inhibitor, Cystatin C, in resting and stimulated human DC. Although the majority of cathepsin activity was restricted to lysosomes in resting DC, cathepsins selectively accumulated in late endosomes after LPS-induced stimulation. Surprisingly, expression and distribution of Cystatin C was unaffected by DC maturation. Thus, late endosomes represent a specialized compartment where proteolytic activity is developmentally regulated in DC. This could facilitate the conversion of exogenous protein into MHC class II-peptide complexes.

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ACCESSION NUMBER: 2003004387 EMBASE
TITLE: Proteinases and their inhibitors in the immune system.
AUTHOR: Van Eijk, Marco (correspondence); Van Noorden, Cornelis Johannes Forrindinis; De Groot, Cornelis
CORPORATE SOURCE: Department of Cell Biology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands.
SOURCE: International Review of Cytology, (2003) Vol. 222, pp. 197-236.
Refs: 231
ISSN: 0074-7696 CODEN: IRCYAJ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jan 2003
Last Updated on STN: 16 Jan 2003

AB The most important roles of proteinases in the immune system are found in apoptosis and major histocompatibility complex (MHC) class II-mediated antigen presentation. A variety of cysteine proteinases, serine proteinases, and aspartic proteinases as well as their inhibitors are involved in the regulation of apoptosis in neutrophils, monocytes, and dendritic cells, in selection of specific B and T lymphocytes, and in killing of target cells by cytotoxic T cells and natural killer cells. In antigen presentation, endocytosed antigens are digested into antigenic peptides by both aspartic and cysteine proteinases. In parallel, MHC class II molecules are processed by aspartic and cysteine proteinases to degrade the invariant chain that occupies the peptide-binding site. Proteinase activity in these processes is highly regulated, particularly by posttranslational activation and the balance between active proteinases and specific endogenous inhibitors such as cystatins, thyropins, and serpins. This article discusses the regulation of proteolytic processes in apoptosis and antigen presentation in immune cells and the consequences of therapeutic interference in the balance of proteinases and their inhibitors. .COPYRGT. 2003, Elsevier Science (USA).

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ACCESSION NUMBER: 2002236660 EMBASE

TITLE: Lysosomal enzymes, cathepsins in brain tumour invasion.
AUTHOR: Levicar, Natasa; Strojnik, Tadej; Kos, Janko; Dewey, Ricardo A.; Pilkington, Geoffrey J.; Lah, Tamara T. (correspondence)
CORPORATE SOURCE: Dept. of Genet. Toxicol./Cancer Bio., National Institute of Biology, Vecna pot 111, 1000 Ljubljana, Slovenia. tamara.lah@uni-lj.si
SOURCE: Journal of Neuro-Oncology, (2002) Vol. 58, No. 1, pp. 21-32.
Refs: 73
ISSN: 0167-594X CODEN: JNODD2
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
029 Clinical and Experimental Biochemistry
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Jul 2002
Last Updated on STN: 18 Jul 2002

AB The expression patterns of different classes of peptidases in central nervous system (CNS) tumours have been most extensively studied in astrocytomas and meningiomas. Although the two types of tumours are very different in most respects, both may invade locally into normal brain. This process of invasion includes increased synthesis and secretion of lysosomal proteolytic enzymes - cathepsins. Aspartic endopeptidase cathepsin (Cat) D levels were found to be elevated in high-grade astrocytoma and partial inhibition of glioblastoma cell invasion by anti-Cat D antibody suggests that the enzyme activity is involved in the invasion process. Several studies on cysteine endopeptidase (CP) Cat B in gliomas agreed that transcript abundance, protein level and activity of Cat B increased in high-grade astrocytoma cultures compared with low-grade astrocytoma cultures and normal brain. Moreover, in glioma biopsies Cat B levels correlated with evidence of clinical invasion and it has been demonstrated that Cat B both in tumour cells and in endothelial cells can serve as a new biological marker for prognosis in glioblastoma patients. A high level of Cat B protein was also a diagnostic marker for invasive types of meningioma, distinguishing between histomorphologically benign, but invasive meningiomas and noninvasive, so-called clear-benign meningiomas. Cat L was also significantly increased in high-grade astrocytoma compared with low-grade astrocytoma and normal brain. Specific Cat L antibodies and antisense Cat L RNA transfection significantly lowered glioblastoma cell invasion. In meningioma, Cat L was a less-significant marker of invasion than Cat B. In contrast to cathepsins, the activities of endogenous cysteine peptidase inhibitors (CPIs), including stefins, cystatins and kininogens, were significantly higher in benign and atypical meningioma cell extracts than in malignant meningioma, and low-grade compared to high-grade astrocytoma. However, very low levels of stefins A and B were found in meningioma and glioblastoma tissues. Further studies on the expression levels and balance between cysteine endopeptidases (CPs) and CPIs would improve the clinical application of cathepsins in prognosis, which would lead to more-informed therapeutic strategies.

ACCESSION NUMBER: 2002075132 EMBASE
TITLE: Multiple roles of the invariant chain in MHC class II function.
AUTHOR: Stumptner-Cuvelette, Pamela; Benaroch, Philippe (correspondence)

CORPORATE SOURCE: INSERM U 520, Institut Curie, 12 rue Lhomond, 75005 Paris, France. benaroch@curie.fr
SOURCE: Biochimica et Biophysica Acta - Molecular Cell Research, (30 Jan 2002) Vol. 1542, No. 1-3, pp. 1-13.
Refs: 150
ISSN: 0167-4889 CODEN: BAMRDP
PUBLISHER IDENT.: S 0167-4889(01)00166-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Mar 2002
Last Updated on STN: 7 Mar 2002

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ACCESSION NUMBER: 2001297533 EMBASE
TITLE: Dendritic cells: Specialized and regulated antigen processing machines.
AUTHOR: Mellman, Ira (correspondence)
CORPORATE SOURCE: Department of Cell Biology, Ludwig Institute for Cancer Research, Yale University School of Medicine, New Haven, CT 06520, United States. ira.mellman@yale.edu
AUTHOR: Steinman, Ralph M.
CORPORATE SOURCE: Laboratory of Cellular Physiology and Immunology, Rockefeller University, New York, NY 10021, United States.
SOURCE: Cell, (10 Aug 2001) Vol. 106, No. 3, pp. 255-258.
Refs: 21
ISSN: 0092-8674 CODEN: CELLB5
COUNTRY: United States
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Sep 2001
Last Updated on STN: 6 Sep 2001

L6 ANSWER 76 OF 78 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2000367359 EMBASE
TITLE: Matrix matters.
AUTHOR: Libby, P., Dr. (correspondence); Lee, R.T.
CORPORATE SOURCE: Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, 221 Longwood Ave, Boston, MA 02115, United States. plibby@rics.bwh.harvard.edu
SOURCE: Circulation, (17 Oct 2000) Vol. 102, No. 16, pp. 1874-1876.
Refs: 15
ISSN: 0009-7322 CODEN: CIRCAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
002 Physiology
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Nov 2000
Last Updated on STN: 13 Nov 2000

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ACCESSION NUMBER: 2000063692 EMBASE
TITLE: Cathepsins and compartmentalization in antigen presentation.

AUTHOR: Riese, Richard J; Chapman, Harold A (correspondence)
CORPORATE SOURCE: Department of Medicine, Brigham Women's Hosp. Harvard M., Boston, MA 02115, United States. hchapman@rics.bwh.harvard.edu
AUTHOR: Chapman, Harold A (correspondence)
CORPORATE SOURCE: Department of Medicine, Brigham Women's Hospital, 75 Francis Street, Boston, MA 02115, United States. hchapman@rics.bwh.harvard.edu
SOURCE: Current Opinion in Immunology, (1 Feb 2000) Vol. 12, No. 1, pp. 107-113.
Refs: 46
ISSN: 0952-7915 CODEN: COPIEL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Mar 2000
Last Updated on STN: 2 Mar 2000

AB Intracellular trafficking and cell surface expression of MHC class II molecules is a tightly regulated process and is to a large extent, determined by the fate of the class II chaperone, the invariant chain. Inhibition of endosomal proteases critical to invariant chain proteolysis reveals marked shunting of class II complexes to lysosomal compartments. Regulation of endosomal protease activity by expression of cystatin C directs class II cell surface expression during maturation of dendritic cells. These studies highlight the taut interactions between class-II-invariant-chain complexes and endosomal proteases during MHC class II maturation.

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ACCESSION NUMBER: 1995220843 EMBASE
TITLE: Peptidyl diazomethanes as inhibitors of cysteine and serine proteinases.
AUTHOR: Shaw, E. (correspondence)
CORPORATE SOURCE: Friedrich Miescher-Institut, CH-4002 Basel, Switzerland.
SOURCE: Methods in Enzymology, (1994) Vol. 244, pp. 649-656.
ISSN: 0076-6879 CODEN: MENZAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Aug 1995
Last Updated on STN: 22 Aug 1995

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